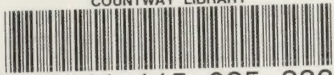


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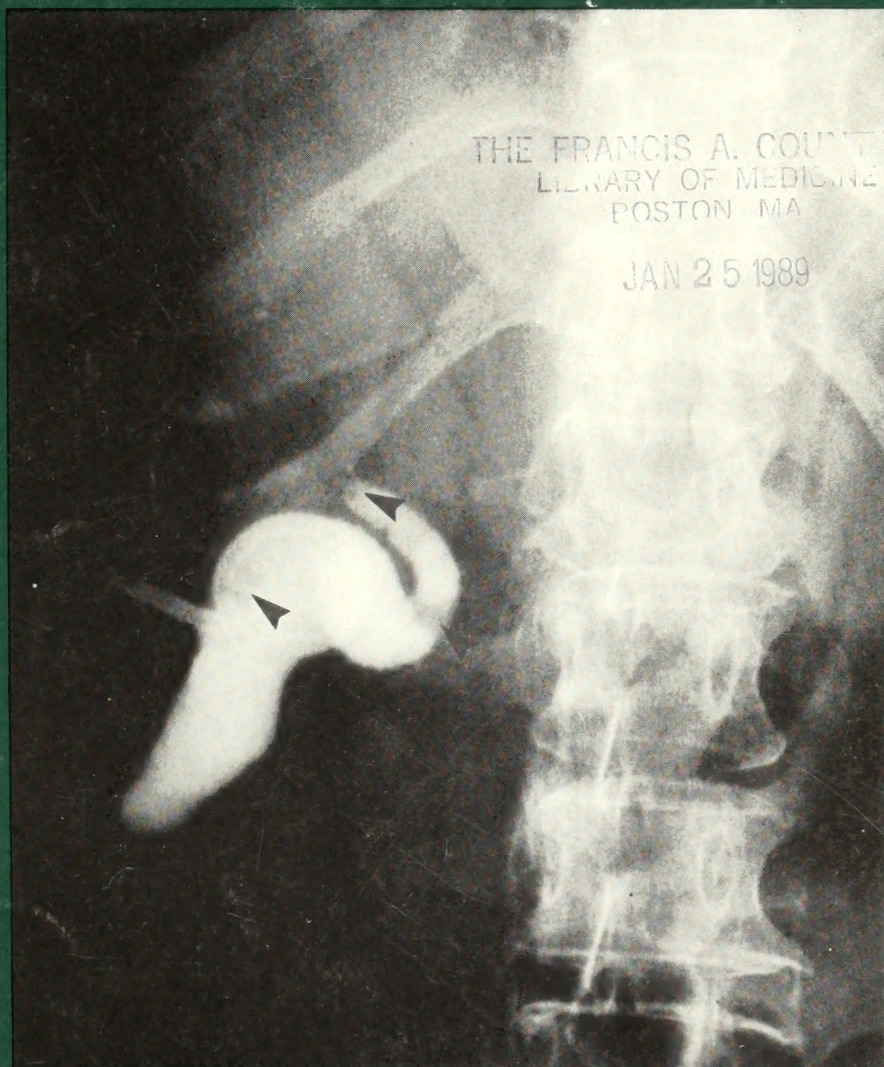
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Volume 72, Number 1



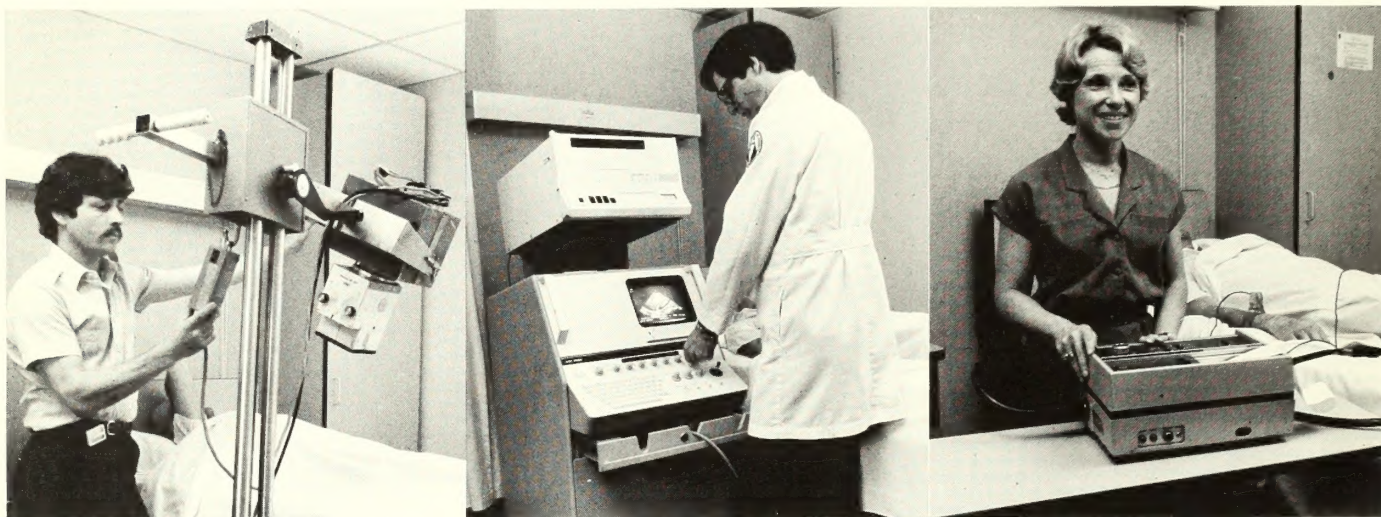
*Tube Cholecystogram
(see page 7)*

*Gallstone Contact Dissolution
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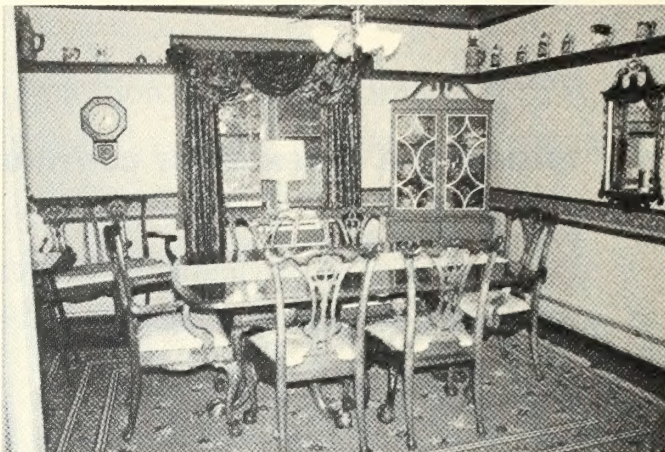
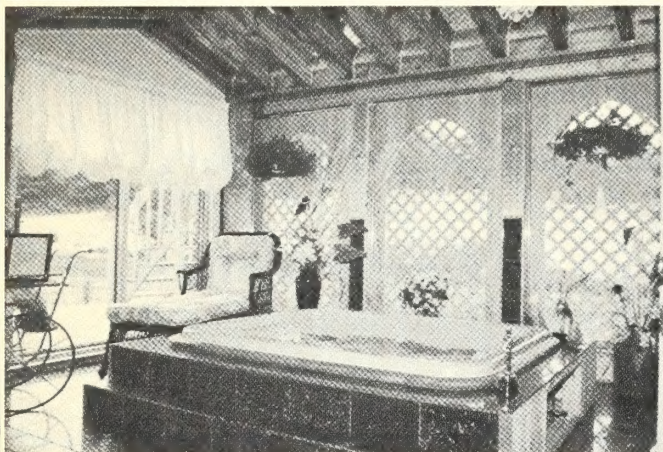
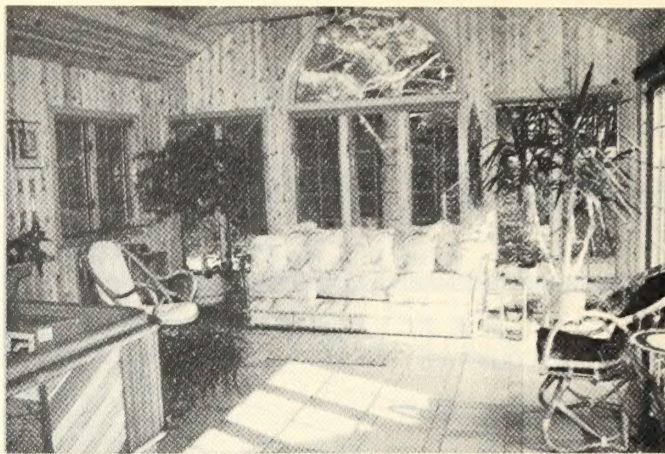
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Cover: Photo of tube cholecystogram courtesy of Departments of Diagnostic Imaging and Surgery, Rhode Island Hospital.

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Antitrust Alert

The unheralded appearance of Assistant US Attorney General Charles F. Rule startled members of the AMA House of Delegates gathered in Dallas in December 1988. Even after Rule had delivered his brief address at the opening of the Tuesday morning session of the House, few delegates fully understood the chain of events that had brought him there. Only later in the morning did AMA Executive Vice President James Sammons take the podium to explain to the House that Rule's visit came on short notice, but was linked to an agreement that the AMA would cooperate with the Justice Department in educating physicians about antitrust issues. In return, certain allergists in Boston, obstetricians in Savannah and dentists in Tucson may be less likely to be indicted for restraint of trade in the near future.

As competition changes the medical marketplace, we are hearing more about antitrust and its ramifications for peer review, medical societies, physician unions, and cooperative medical practice arrangements of all kinds. Physicians are feeling confused and threatened by these murky new dangers.

Rule suggested a few basic guidelines that he thinks will help physicians void antitrust trouble. He admonished them not to agree with competing independent physicians "on any term of price, quantity, or quality, . . . on the patients you are willing to serve, the locations from which you are permitted to draw patients, or where you will locate your offices," or on refusing "to offer your services to alternative delivery systems." He made it explicitly clear that the public interest in quality was not within the province of the Justice De-

partment. "Today antitrust enforcement policy is focused solely on preventing conduct that threatens to raise prices to consumers," he said. "Never think you have the right by whatever private means to override the forces of competition, even where they do not seem to be providing sufficient quality or sufficient remuneration. If consumers' preferences, as expressed through the voice of the marketplace, are for low-cost rather than traditional fee-for-service medical care, you may not overcome those desires by agreement among yourselves. Those decisions are for Congress alone to make."

For better or worse, we as a nation have decided that competition shall shape the delivery of medical care. The decision is reinforced by the perception that care costs too much and the faith that free-market competition controls costs. The day may come when Americans decide that our national health policy should be driven more by professional medical judgment and issues of quality patient care than by cost concerns alone. In the meantime, we are all likely to get a great deal more education about the Sherman Antitrust Act.

What is competition? In the words of Princeton economist Uwe Reinhardt, "Competition means that life is hell on earth for providers, while it is cheap and easy even for dumb consumers." At least half of Professor Reinhardt's definition seems applicable to American medicine today.

Newell E. Warde, PhD
Executive Director
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Success of Contact Chemolysis in Calcified Cholesterol Gallstones

Dissolution Accomplished in the Face of Combined Obstructing and Non-Obstructing Calculi

Evan Geller, MD
John J. Cronan, MD
Gary S. Dorman, MD
Michael Rocchio, MD

Methyl tertiary butyl ether (MTBE) is an aliphatic ether that has received recent attention as a cholesterol gallstone contact dissolution agent. Although structurally related to diethyl ether, it remains in a liquid state at body temperature.¹ It rapidly dissolves cholesterol gallstones both *in vitro* and *in vivo*¹⁻³ and compares favorably with the currently accepted agent of choice, monooctanoin (MO). We report our initial experience with MTBE following percutaneous cholecystostomy in a patient deemed a poor surgical candidate for cholecystectomy.

CASE REPORT

AR, a 60-year-old white female, was hospitalized on numerous occasions for recurrent episodes of biliary colic and acute cholecystitis. She was considered a poor surgical risk because of an extensive history of coronary artery disease. A conservative course of medical management was implemented during each admission (fat-free liquid diet, intravenous hydration, and antibiotics) with a gradual abatement of symptoms. Other significant medical history included non-insulin dependent diabetes mellitus, hyperlipidemia, and non-A non-B hepatitis believed to have been ac-

quired as a result of repeated blood transfusions during previous coronary artery bypass surgery.

Diagnostic imaging studies performed prior to her current hospitalization included two unremarkable right upper quadrant ultrasound examinations in 1984 and 1985 following episodes of right upper quadrant pain. One month prior to the present admission she again presented with symptoms of post-prandial abdominal discomfort and nausea. A repeat ultrasound at that time demonstrated multiple gallstones (Figure 1). Subsequent Technetium Disofenin (DISIDA) scan was significant for non-filling of the gallbladder at four hours despite normal transit of tracer activity through the biliary tree and into the small bowel, compatible with a diagnosis of acute cholecystitis (Figures 2A, 2B). The patient's most recent admission in June 1987 was precipitated by severe post-prandial pain and nausea. Body temperature was mildly elevated at 100°F rectally. On physical examination both voluntary guarding and rebound tenderness were elicited. Laboratory data were unremarkable except for a mild leukocytosis of 11,100 white blood cells per mm³, and a chronically elevated serum glutamic oxaloacetic transaminase of 41 IU/L (range 5-31) and serum glutamic pyruvate transaminase of 57 IU/L (range 5-31). Gamma glutamyl transpeptidase was minimally elevated at 30 IU/L (range 5-29). Serum amylase, alkaline phosphatase, and total bilirubin were normal. An admission erect plain film of the abdomen demon-

The authors of the following article are with the Departments of Diagnostic Imaging and Surgery at Rhode Island Hospital and Brown University Program in Medicine, Providence, Rhode Island.

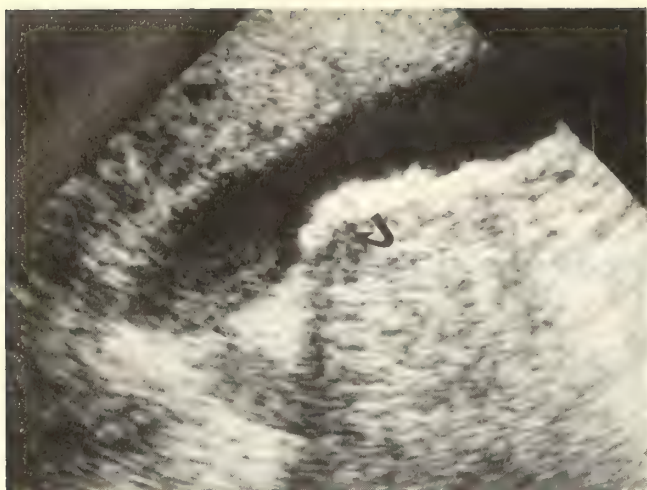


Fig. 1. Sagittal ultrasound of gallbladder demonstrating numerous echogenic foci with shadowing (arrow) compatible with gallstones.

strated layering calcific densities in the right upper quadrant presumed to represent gallstones. The patient was managed with intravenous antibiotics and appropriate dietary modifications resulting in a prompt defervescence and a more gradual abatement of her abdominal symptoms.

Because of the increasing frequency of the attacks, the potential risk of progression to gangrenous cholecystitis, and clear-cut contraindications to surgical intervention, it was elected to perform a percutaneous cholecystostomy for the immediate purpose of decompression and subsequent gallstone chemolysis when the acute process had subsided.

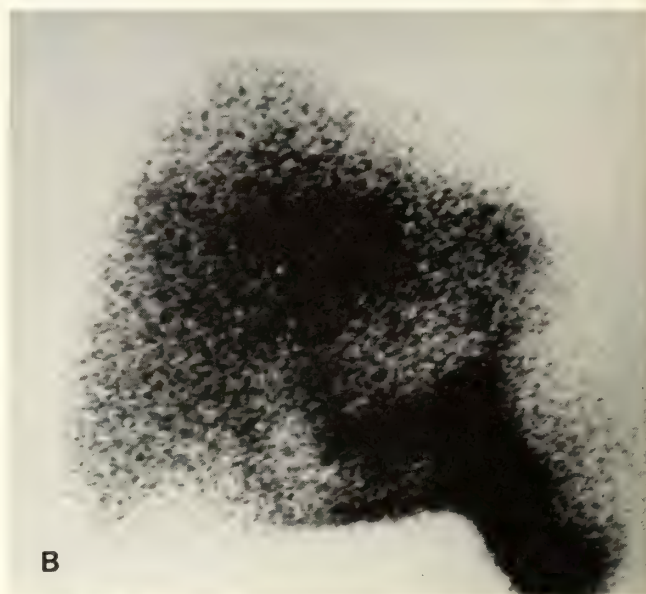
Percutaneous cholecystostomy was accomplished in an uneventful fashion on the sixth day of admission. Under computed tomography (CT) guidance, a number 8 French biliary drainage catheter was placed percutaneously into the gallbladder lumen utilizing a transhepatic approach. Very thick tenacious bile was aspirated. A cholecystogram performed via the drainage catheter demonstrated multiple stones surrounding the coiled catheter tip within the gallbladder fundus as well as stones within the neck of the gallbladder (Figure 3). No contrast entered the common bile duct due to complete cystic duct obstruction. The indwelling catheter was left to gravity drainage.

Tube drainage was minimal (25 ml total) over the ensuing 48 hour period, and a repeat tube cholecystogram demonstrated no change in the number or location of gallstones. The tube was exchanged for a number 10 French nephrostomy catheter, and aspiration yielded an ex-



Fig. 2A. One hour DISIDA scan demonstrating persistent bile duct activity and activity within the duodenum. No gallbladder visualization is noted.

B. Four-hour DISIDA fails to show gallbladder activity.



tremely thick, dark "crankcase oil" material which gradually changed in nature to a mildly hemorrhagic material of lower viscosity with gentle repetitive irrigation. Numerous small white stone fragments were contained in the aspirated material. The patient was returned to the nursing

unit on an intermittent saline irrigation schedule.

Gallstone contact dissolution with MTBE was begun on the eleventh day of drainage. Care was taken to conduct prior *in-vitro* testing of the various components of the closed delivery and exhaust system *vis-à-vis* prolonged exposure to MTBE, and to avoid the use of a percutaneous catheter (Medi-tech, Watertown, Mass) as a conduit for MTBE. This precaution was taken to insure the integrity of the system when exposed to MTBE.⁴ Following an initial tube cholecystogram and with the patient in a semi-upright position, MTBE infusion was begun by instilling 5 ml into the polyethylene catheter then withdrawing it after five minutes. This regimen was continued for a period of 1 1/2 hours and was gradually increased to a 10 ml infusion with withdrawal after ten minutes for a 2 1/2 hour period and finally to a 15 ml infusion with withdrawal after 10 minutes for an additional 30 minutes. Vital signs were monitored very closely throughout the procedure. Tube cholecystograms repeated midway through the procedure and at the end of the day demonstrated a decrease in the total number of gallstones and an increase in stone mobility in the region of the gallbladder neck. The patient experienced no adverse effects over the course of these 4 1/2 hours.



Fig. 3. Tube cholecystogram shows pigtail catheter in gallbladder and numerous stones in the body of gallbladder and in the neck of the gallbladder (arrowheads). An additional stone is causing total obstruction of the cystic duct (arrowhead).

The following morning MTBE infusion was reinstituted without first performing a cholecystogram. Approximately one minute following initial installation of 15ml MTBE, the patient became markedly diaphoretic, transiently hypotensive, bradycardic (to below known baseline bradycardia) and somnolent with the distinctive smell of ether detected on her breath. She responded quite rapidly to resuscitative measures including intravenous hydration, Trendelenburg positioning, and prompt removal of instilled MTBE. Repeat tube cholecystogram (Figure 4) revealed for the first time unimpeded drainage of contrast material into the common bile duct and duodenum with complete dissolution of all gallstones (a small persistent filling defect within the midcystic duct was felt to represent either a kink or focal area of fibrosis upon several subsequent tube cholecystograms).

The patient was discharged to her home the following day on a daily regimen of chenodeoxycholic acid. The cholecystostomy tube was left in place and continued to drain externally. She returned on two other occasions for catheter checks and change. After a trial week with the tube capped, it was removed. A repeat ultrasound study at that time demonstrated a normal appearing gallbladder without evidence of residual calculi.

Discussion

Contact dissolution of cholesterol gallstones is not new. There is a report in the literature of 1891 utilizing ether as a chemolytic agent.⁵ Since the 1930s, a large body of *in-vivo* studies has been accumulated regarding gallstone contact dissolution employing a variety of agents including warm saline and olive oil,⁶ ether,⁷ chloroform,⁸ heparin,⁹ sodium cholate,¹⁰ and various combinations of the above, all of which have been abandoned because of ineffectiveness or potentially serious local or systemic toxicity. Routes of administration have been variable and have included: an intraoperatively placed biliary drainage catheter following cholecystectomy and choledochotomy,^{7,9,11} through a nasobiliary catheter positioned within the common bile duct or into the hepatic ducts,¹² or via a percutaneously placed cholecystostomy^{4,12} or choledochostomy¹³ tube.

Since 1980 two agents have dominated the field of gallstone chemolysis: glycerol-1-monooctanoate (mono-octanoate) and more recently methyl tertiary butyl ether (MTBE). Following initial *in-vivo* canine trials of gallstone contact dissolution with MTBE¹ it became apparent that MTBE of-

ferred a distinct advantage over mono-octanoin (MO) in rapidity of action. MTBE is capable of dissolving cholesterol gallstones 50 times faster than MO, with an average duration of therapy approximating 4 to 16 hours in contrast to the 3 to 21 days necessary for MO.¹ In our patient complete stone dissolution occurred after a 4 1/2 hour infusion period.

Side effects of MTBE have been variable and have ranged from mild and transient elevation of liver enzymes following catheter removal¹² to burning abdominal pain and heavy sedation during actual infusion.⁴ Frank leakage of solvent into the peritoneal cavity or hepatic parenchyma following percutaneous gallbladder puncture has thus far not been reported. As described earlier, our patient experienced a vasovagal-type episode accompanied by heavy sedation following instillation of a large volume of MTBE into the gallbladder on day two of therapy. This was presumed to be the result of the rapid systemic absorption of MTBE upon entry into the duodenum. Duodenal passage of MTBE was not encountered during the initial treatment phase because a stone was impacted within the cystic duct. This event clearly illustrates the necessity for performing tube cholecystography at reasonably frequent intervals during MTBE infusion to assess any change in cystic duct or common duct patency. Our experience also illustrates that relatively large volumes of MTBE (up to 15 ml or

the approximate gallbladder capacity) may be infused at any one time without adverse systemic effects provided that there is complete cystic duct obstruction.

Whereas others have demonstrated the utility of MTBE as a contact dissolution agent in the setting of multiple, relatively small non-obstructing gallbladder calculi¹² as well as in the setting of a solitary large gallbladder calculus causing complete obstruction of the cystic duct,⁴ this represents to our knowledge the first reported case documenting the therapeutic efficacy of MTBE in the face of both non-obstructing as well as obstructing gallbladder calculi.

Although it has been recommended that contact dissolution with MTBE be attempted only with radiolucent gallstones,¹⁴ we as well as others¹⁵ have documented its efficacy even when stones are calcified, so-called "type I"¹⁶ cholesterol gallstones. Seventy to 80 per cent of gallstones in the western world are composed mainly of cholesterol. In the United States, approximately 50 per cent to 70 per cent of all gallstones are Type I stones and 33 per cent of these may have radiographically detectable calcifications.¹⁶ The suggestion that one is dealing with calcified gallstones should not serve as a deterrent to MTBE-infusion therapy. Furthermore, by employing a multivariant model using gallstone buoyancy, size, calcification-pattern and stone-surface characteristics as set forth by Dolgin et al¹⁷ or by performing duodenal bile aspiration and analysis of the chemical composition following gallbladder stimulation, one may considerably augment the likelihood that a calcified gallstone or group of stones is composed predominantly of cholesterol and not bilirubinate. This is an important distinction which would considerably alter the course of therapy, as pigment stones are refractory to conventional MO and MTBE therapy.

While as yet an unproven technique, in the proper clinical setting cholesterol gallstone dissolution with MTBE may serve a minor role as an invaluable alternative to surgery. Multiple gallstones, obstruction of the cystic duct or radiographically detectable calcification (separately or in concert) should not dissuade one from this form of therapy in an appropriate patient. Most encouraging thus far has been its therapeutic efficacy and record of safety.

Summary

Contact dissolution of cholesterol gallstones has emerged as a viable alternative in patients at high risk for surgery. The newest dissolution agent



Fig. 4. Tube cholecystogram on second day of MTBE therapy shows total dissolution of gallstones and unimpeded drainage of contrast material into common bile duct. Persistent cystic duct defect (arrow) is evident.

methyl tertiary butyl ether (MTBE) has undergone a series of successful clinical trials and has compared favorably with its predecessor, mono-octanoin (MO). Previous studies have demonstrated the utility of MTBE in the setting of a large solitary gallstone impacted within the cystic duct as well as with multiple non-obstructing gallstones. We present a case of MTBE contact dissolution in the face of combined non-obstructing and obstructing gallbladder calculi. Whereas others have recommended restricting its use to those gallstones that are radiolucent, we have shown that MTBE may be used, and excellent results obtained, even with calculi that are calcified, so-called "Type 1" cholesterol gallstones.

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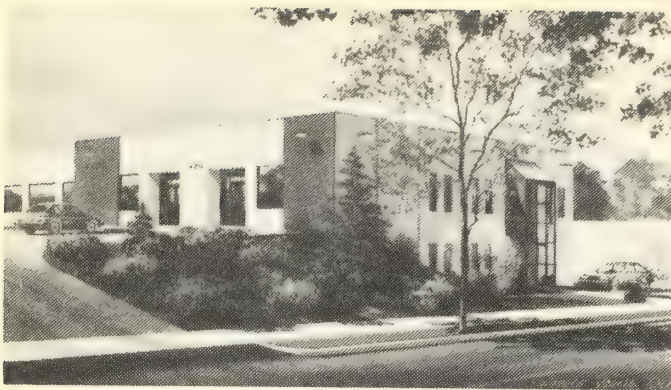
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BRIEF SUMMARY

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PRECAUTIONS

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Drug Interactions: Animal studies have shown that simultaneous administration of CARAFATE (sucralfate) with tetracycline, phenytoin, digoxin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. This interaction appears to be nonsystemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The clinical significance of these animal studies is yet to be defined. However, because of the potential of CARAFATE to alter the absorption of some drugs from the gastrointestinal tract, the separate administration of CARAFATE from that of other agents should be considered when alterations in bioavailability are felt to be critical for concomitantly administered drugs

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted

Pregnancy: Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients treated with sucralfate, adverse effects were reported in 121 (4.7%).

Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

OVERDOSAGE

There is no experience in humans with overdosage. Acute oral toxicity studies in animals, however, using doses up to 12 gm/kg body weight, could not find a lethal dose. Risks associated with overdosage should, therefore, be minimal.

DOSAGE AND ADMINISTRATION

The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

HOW SUPPLIED

CARAFATE (sucralfate) 1-gm tablets are supplied in bottles of 100 (NDC 0088-1712-47) and in Unit Dose Identification Packs of 100 (NDC 0088-1712-49). Light pink scored oblong tablets are embossed with CARAFATE on one side and 1712 bracketed by C's on the other. Issued 1/87

Reference:

1. Eliakim R, Ophir M, Rachmilewitz D: *J Clin Gastroenterol* 1987;9(4):395-399.

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For respiratory tract infections due to susceptible strains of indicated organisms.

Summary.
Consult the package literature for prescribing information.

Indication: Lower respiratory infections, including pneumonia, caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Streptococcus pyogenes* (group A β -hemolytic streptococci)

Contraindication: Known allergy to cephalosporins.

Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS

Administer cautiously to allergic patients
Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis

Precautions:

- Discontinue Ceclor in the event of allergic reactions to it
- Prolonged use may result in overgrowth of nonsusceptible organisms
- Positive direct Coombs' tests have been reported during treatment with cephalosporins
- Ceclor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in

moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.

- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis

- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients

Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include

- Gastrointestinal (mostly diarrhea) 2.5%
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] and toxic epidermal necrolysis or the above skin manifestations accompanied by arthritis/arthritis, and frequently fever) 15%, usually subside within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome

- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy
 - As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely
 - Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonemia, dizziness, and somnolence have been reported
 - Other: eosinophilia, 2%, genital pruritus or vaginitis, less than 1%, and, rarely, thrombocytopenia
- Abnormalities in laboratory results of uncertain etiology**
- Slight elevations in hepatic enzymes
 - Transient fluctuations in leukocyte count (especially in infants and children)
 - Abnormal urinalysis, elevations in BUN or serum creatinine
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Non-Ionizing Electromagnetic Radiation and Cancer — Is There A Relationship?

The Ubiquity of Electromagnetic Radiation with its Possible Health and Carcinogenic Potential Suggests a Research Agenda

Joseph R. Salvatore, MD
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The evolution of plant and animal species over millions of years undoubtedly has been affected by, and occurred in concert with, electromagnetic radiation (EMR) which bathes the earth in its many forms. Although the interaction between EMR and living organisms has long been recognized, only in the last few hundred years — with concurrent increasing man-made EMR and scientific sophistication — has an interest in elucidating the nature of this interaction arisen. In this paper we shall review current information about EMR, its interaction with living organisms, particularly human beings, and its possible carcinogenic potential.

Electromagnetic Radiation

EMR can be thought of as waves and packets of energy which are normally categorized according to the number of completed full cycles in one

second, also called its frequency. The concept of packet and wave is an important one because it is believed that the particular nature of the wave is responsible for much of its biologic action.¹ At the lower end of the spectrum are the extremely low frequencies of energy carried in power lines, 60 Hertz (Hz) or cycles per second, while at the higher end are waves such as x-rays used in radiation therapy. In between these extremes is EMR represented by radiowaves and microwaves.

The energy associated with EMR ranges from very low energy represented by radiowaves to very high energy represented by instrumentation used in radiation therapy. Distinction between these low and high energy levels is important because it represents the difference between non-ionizing and ionizing radiation respectively. Ionization occurs when the electromagnetic wave possesses sufficient energy to knock electrons out of their orbits. This energy or "photon energy" is directly proportional to the frequency of the electromagnetic wave.² Therefore, with increasing frequency there is increasing potential for atomic and molecular disruption, i.e. ionization. Energy in EMR is measured in eV (electron-volts). As a means of comparison, penetrating x-rays of a frequency of 10^{20} Hz generate 4.12×10^5 eV, light of a frequency of 6×10^{14} Hz generates 2.47 eV, and microwave radar at 10^{10} Hz generates 4.12×10^{-5} eV.³ Radio waves generate less energy than microwaves.

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If non-ionizing radiation does not create ions in tissue by moving electrons out of orbits as ionizing radiation does, how does it interact? There are two perceived modes of action: 1) by creating an increase in the heat within the affected tissue, a "thermal" effect, and 2) through an "athermal" effect, interacting with the tissue without creating an increase in temperature.⁴ This second effect is much less well defined, and research is being carried out to study its interactions and possible carcinogenicity.

Historical Perspectives — Animal Data

In the late 1700s, the action of electricity on living tissue was demonstrated by Galvani. He noted that dissected frog muscle which was in contact with a strip of metal would twitch when a spark of electricity was generated nearby, but not in contact with the metal strip.⁵ Volta and others showed in further experimentation that Galvani's work was reproducible, but great controversy surrounded the nature of this "animal electricity."⁵ D'Arsonval, at the turn of this century, used electricity to elucidate the workings of muscle contraction. By applying current with frequencies approaching 2.5 KHz, muscular contraction became more intense and sustained, a condition called tetanization. Among his most important observations, however, was the fact that, when applied current had a frequency greater than 10 KHz, warmth but no contraction was generated.⁵ Medical science would recognize in later years that electromagnetics could be used to study the human being in disease and health with instruments such as the electrocardiograph, electroencephalograph, and echocardiograph. Electroshock therapy would be used in the treatment of psychiatric illness.

An early account of a physician observing the effects of electric current was published in the *Lancet* in 1880.⁶ Dr A. Allison describes a farm laborer who had cancer of the lip and chin for about one year. While working in the fields he was struck by lightning, and, when examined, the patient emitted a "strong odor of ozone." The patient was bled immediately and over a two week period. The tumor regressed completely. He remained disease free for about ten years. Dr Allison called upon the London Cancer Hospital to conduct tests of electro-treatment.

Early reports of experimentation with EMR included

Szent-Gyorgi⁷ in 1933 exposed Ehrlich's carcinoma cells to 7.23 KHz and reported no specific

effect. Payne-Scott in 1936 exposed chick embryo heart cells in tissue culture to magnetic fields of 5000 gauss and concluded that, although there were no visible chromosomal abnormalities in dividing cells, resting cells showed "protoplasmic disintegrations."⁸ Lenzi in 1940 published what appeared to be a scientifically based study using exposure to varying frequencies of magnetic field with field strength of 1500 to 1700 gauss.⁹ Exposure of wounds or bone wounds to magnetic fields produced no appreciable difference in reparation. However, mice to which Ehrlich's carcinoma was grafted showed a delay in the "take" of the neoplasm when exposed to magnetic fields. Neither constant nor alternating magnetic fields appreciably changed tumors already "taken." MacLean in 1959 published a preliminary report on the effects of intense and mild permanent magnetic fields on C3H strain mice.¹⁰ Due to the lack of detail in this paper concerning experimental design it is difficult to accept conclusions with certainty.¹⁹

Heller in 1959 described using pulsed 27 MHz radiation to create chromosomal aberrations in garlic root tips.¹¹ He took care in the experimental design not to increase the temperature of the water in which the root was growing. Interestingly, the author pointed out that the aberrations noted were similar to those created by ionizing radiation. Halpern in 1964 examined the effects of magnetic fields on HeLa Cells in tissue culture with exposure to 1200 gauss for two-seven days and concluded that no inhibition or other overt effect was observed.¹² Halpern also pointed out that Gerencser in 1962 had reported inhibition of growth of *S marcescens* and *S aureus* by exposure to 15,000 gauss when compared to controls but not until five-eight hours after exposure.¹³ Levengood in 1966 designed a magnetic probe which provided a non-homogeneous intense magnetic field generating 9000 gauss per mm at 2 mm from the probe tip. *Drosophila* gonadal organs were irradiated, and the reported effects included growth retardation which, even though pupae producing the first generation were exposed, was transferred to succeeding generations. Importantly, no significant heating was noted with exposures of at least 30 minutes.

Malinin in 1976 published evidence that strong magnetic fields could transform mammalian cells morphologically and physiologically.¹⁵ In this work, heteroploid L-929 and diploid WI-38 cells were exposed to 5000 oersteds for four-eight hours while frozen at -90 degrees centigrade. After thawing, control and exposed cells were

cultured. Exposed cells showed: 1) inhibited growth, 2) tightly packed aggregates, and 3) formed ridges several layers deep. The authors concluded that exposed cells lost contact inhibition. Additionally, the authors noted cellular changes which they termed "transformed," although they pointed out that this term did not imply neoplastic transformation. The Mayo Clinic in 1948 reported the first confirmed adverse effects believed to be due solely to microwaves, cataractogenesis in dogs.¹⁶ Simultaneous work done at the University of Iowa showed a possible link between microwaves, cataracts, and testicular degeneration in dogs. John McLaughlin in 1953, a medical consultant, in a report to the military, suggested that microwave radiation may have effects such as purpura hemorrhagica (internal bleeding), leukemia, cataracts, headaches, brain tumors, heart conditions, and jaundice.¹⁶

A few animal studies have been conducted to answer directly whether microwave radiation is carcinogenic. Preskorn in 1978 published data which centered around implantation of a homogenate of lymphoreticular cell sarcoma with pre- and post-implantation 2450 MHz microwave radiation in CFW mice.¹⁷ In the first part of the study the fetal mice were irradiated both in utero and post-implantation, and colonic temperatures of the pregnant females increased on average 2.24 degrees centigrade. The authors believed that the elevation of body temperatures by the microwave radiation probably enhanced immunocompetency and both delayed the onset of experimental neoplasms and reduced the mortality of tumor bearing animals.

Szmigielski in 1982 reported acceleration of benzopyrene-induced skin cancer in mice by the addition of exposure to 2450 MHz microwave radiation.¹⁸ However, the authors also suggest the possibility that, because small rodents appear able to perceive even weak microwaves, the observed acceleration may be due to a stress, or adaptation reaction, or both. They also point out that, due to certain differences in rates of energy absorption, the mouse model has inherent limitations in its ability to predict microwave hazards in human subjects. Balcer-Kubizek treated mice fibroblast cells with 2.45 Ghz (Gigahertz) microwave radiation in combination with benzopyrene or x-rays and found a significant enhancement of transformation frequency in certain treated subgroups.¹⁹ In the cells treated with microwaves and x-ray, a group was then cultured with 12-O-tetradecanoylphorbol-13-acetate (TPA) in what was reported as a non-transforming concentra-

tion. These cells showed a significant enhancement of transformation. Cells not cultured with this tumor promoter showed no increase in transformation. The authors conclude that low level microwaves at 2.45 GHz induce latent transformation damage which is then expressed by the action of tumor promoters.

Leukemia and lymphoma appear to be the malignant conditions most commonly found in this association. . . .

Human Studies

A series of studies over the past ten years have been carried out in an attempt to relate exposure to electromagnetic radiation in various forms to an increased incidence of human cancer. Leukemia and lymphoma appeared to be the malignant conditions most commonly found in this association, although primary nervous system malignant disease has also been suggested. Zaret, using information which was anecdotal, noted a possible relationship between exposure to microwave radiation (radar) and cancer, especially pancreatic cancer.²⁰

Wertheimer and Leeper in 1979 studied the possibility that magnetic fields generated by high current power lines were somehow related to childhood cancer, particularly leukemia in the Denver, Colorado area.²¹ They pointed out that the study contains no specific attempt to take direct measurements of magnetic fields at the homes that were studied, but instead based the study on what they perceived as the potential current flow suggested by various wiring configurations. Wiring near homes studied in both cases and controls was divided into high current configurations (HCC) and low current configurations (LCC). The authors' data showed a correlation between the HCC and cancer deaths primarily from leukemia. The authors suggested a number of possible explanations for their findings including the concept that strong magnetic fields may either cause malignant disease directly or promote it indirectly.

Fulton et al the following year were unable to duplicate these results.²² They concluded that there was no relationship between leukemia and electric power line configurations.

Wertheimer in a critique of Fulton's data claimed that re-analysis using the HCC/LCC designations put forth previously showed a modest association between HCC and cancer.²³ A further

critique of Fulton's study by Bryan concluded that two assumptions made in the study brought the conclusions into question.²⁴ Wertheimer in 1982 in a second study of the relationship between electric power line magnetic fields turned her attention to adult cancer cases.²⁵ Again, using divisions of wires to devise a classification scheme that included very high current configurations (VHCC), ordinary high current configurations, and ordinary low current configurations, the authors were able to conclude that for VHCCs the proportion of homes where cancer cases were found was greater than in control homes. Four types of cancers were noted in significantly higher numbers: nervous system, endometrial, breast, and lymphoma. Though the association was significant, the authors were of the opinion that this was weaker than for the childhood cancer. They concluded from this study that there was both an apparent dose relationship and a pattern of latency consistent with tumor promotion.

(The Spitz) study concluded that children whose fathers were employed in occupations with electromagnetic field exposure were at significantly increased risk.

A more recent study in Sweden by Tomenius attempted to correct the inconsistency noted in previous studies by measuring levels of magnetic fields.²⁶ Current flow was determined not only by direct observation, but also by measuring 50-Hz magnetic fields at the front entrances of dwellings of both cancer cases and controls. In this study childhood cancers for subjects up to 18 years of age were also observed. The Tomenius study data did not confirm an excess risk for leukemia (which was similar to Fulton's conclusions). There appeared to be a relationship between the incidence of neoplasia and increased magnetic fields greater than or equal to 0.3 microtesla (μ T). This, however, was significant only for nervous system tumors. The relationship between exposure to electromagnetic fields and nervous system tumors had been reported previously. Spitz in 1985 reported on a relationship between neuroblastoma and paternal occupation.²⁷ Since the peak incidence of neuroblastoma is during infancy (50 per cent under two years of age), the authors suggest that prenatal or prezygotic influences may have an important role in the pathogenesis of the disease. Their study concluded that children whose fa-

thers were employed in occupations with electromagnetic field exposure were at significantly increased risk.

Lin also in 1985 studied the relationship between exposure to EMR and the incidence of brain tumors in white males 20 years old and older.²⁸ Mortality rate for brain tumor was selected because it was believed that this group of disorders would be difficult to misclassify and the diagnosis on death certificates would therefore be accurate. The authors chose categories of occupation based on the presumed exposure to the EM fields. Their results suggested that, especially in the glioma-astrocytoma group, there were a greater than expected number of brain tumor deaths in electricity-related occupations. Additionally, glioma-astrocytoma patients in group A (definite exposure) died at significantly younger ages than those in group D (no exposure). The authors suggested that their data are in agreement with others (Easterly, 1981 and Wertheimer and Leeper, 1982) that non-ionizing radiation may be a tumor promoter.

Between 1982 and 1985 a series of studies was published which linked occupational exposure to electromagnetic fields in workers in electrically-related occupations to an increased rate of cancer, particularly leukemia. Milham used proportionate mortality ratios (PMR) and found more deaths from leukemia in workers exposed to electric and magnetic fields than those not exposed.^{29, 30} He concluded that EM fields may be leukemogenic. Milham has also implicated that this suggested leukemogenic property is responsible for increased PMR of acute and chronic myeloid leukemia (AML and CML) among amateur radio operators.³¹ Wangler has criticized this conclusion, as have Seager and Currier.³²⁻³⁴ An updated version of Milham's data³⁵ published in 1988 offers the same conclusion, that this group is subject to higher mortality from AML.

Wright's study reviewed leukemia in men who were listed as having jobs with exposure to electric and magnetic fields at the time of diagnosis.³⁶ Wright's work, however, differed from Milham's in that Wright used proportional incidence ratios (PIR) instead of PMRs but also concluded that numbers were highest for AML. He also pointed out that the issue is clouded by the fact that these workers may also be exposed to chemical carcinogens such as benzene and fluxes.

After reviewing the above studies, McDowall used PMRs to analyze occupational mortality and electrical occupations.³⁷ He concludes that these analyses agree with the data of the other two

studies. McDowall points out, however, that there is inconsistency between the studies in terms of degree of risk for the electrical occupations chosen and mobility between occupations making it difficult to interpret the data. Coleman using the ten occupations analyzed by McDowall found a 17 per cent excess of all leukemias for all ten occupations.³⁸ The excesses were noted for AML, acute lymphocytic leukemia (ALL), and chronic lymphocytic leukemia (CLL) but not CML. While the excess level was significant for two occupations, electrical fitters and telegraph/radio operators, radio and radar mechanics had a deficit of all leukemias. The author felt that these data were broadly consistent with the three previous studies.

Pearce noted an excess of leukemia in electrical workers while reviewing a case control study of leukemia and agricultural occupations.³⁹ For occupations with exposure to alternating current fields, an excess of leukemia cases was found in electronic equipment assemblers and radio/tv repairmen. The author notes that the numbers were too small to investigate risk for the specific leukemias, but the findings support in general terms the possibility of increased risk of leukemia in electrical workers.

Finally, Barregard studied cancer incidence in workers in a chloralkali plant.⁴⁰ Direct current of 100 kiloamps (kA) used in the process of producing chlorine by electrolysis produces strong static magnetic fields. The cancer incidence in men in the Swedish county where the plant is located, was compared to the expected cancer incidence in Swedish men in general. No increase in mortality of exposed subjects was found, and the incidence of cancer was not increased. This study, it should be emphasized, had to do with static magnetic fields as compared to other studies where the subjects were exposed to power line fields which carry alternating current.

These studies have been criticized in both the medical and engineering literature. Liburdy characterized Milham's 1982 suggestion that EM fields are carcinogenic as "alarmism."⁴¹ An editorial review in the *Lancet* in 1983 of studies to that date expressed the view that clusters of AML were worrisome, but pointed out that the evidence was inconsistent.⁴² It also noted that much of the evidence was based on PMRs, which, theoretically, can be misleading. Most of the criticism of these studies, however (including those of Wertheimer and Leeper) centers around a few basic design and interpretation problems. In almost all studies there is a lack of quantification

of the strength of fields involved as well as length of exposure to the EM fields, and these appear to be repeatedly acknowledged as major limiting factors in these studies.⁴³⁻⁴⁶ Further, there is a failure to account in a systematic way for other agents, including chemicals and fumes, which may be considered carcinogenic.⁴³⁻⁴⁵ Currier in a criticism of Milham's study of amateur radio operators points out that other health related factors such as smoking, obesity, diet, and alcohol intake must be considered.³⁴

These studies have been criticized in both the medical and engineering literature.

The epidemiologic and statistical methods used to arrive at conclusions in these studies, including PMR, PIR, death certificates, and nature of the control group, all can generate misleading information.⁴⁶⁻⁴⁸ As Shiekh points out, higher proportionate mortality from one cause may be due to lower proportionate mortality from other cases.⁴⁷ Finally, there is a mixture of frequencies, as well as variations in the use of electric versus magnetic fields, which makes comparison difficult. Some studies and reviews, including the studies of Fulton and Barregard, have shown no clear-cut health hazard, particularly no increase in the risk of developing cancer.⁴⁹ Robinette studied the effects of microwave radiation (radar) on the health of military personnel from the Korean War with exposure from 1950-1954.⁵⁰ He included 20,000 subjects with "maximum" exposure and 20,000 with "minimum" exposure. He reports that no adverse effects were detected that were attributable to presumed microwave exposure during this period; and he also noted that the exposure was potentially rather than actually measured. Calle in 1985, after studying mortality data for the ten electrical occupations used by Milham and Wright, reported that no pattern of excess mortality from leukemia was found.⁵¹ McDowall in 1986 reported on the mortality of 8,000 persons who were identified as living in the vicinity of electrical transmission facilities.⁵² The study concluded that there was no evidence to indicate a major health hazard and that the data did not support the previously reported association of exposure to EM fields with AML and lymphatic cancers.

Concern over the possible health effects of EM radiation generated by current carried in power transmission lines prompted the state of New

York to conduct the New York Power Lines Project's study "Biological Effects of Power Line Fields." The final report was released in July, 1987.⁵³ Among its studies, the relationship between EM radiation and cancer was examined both *in vitro* and in epidemiologic studies. Clonogenicity of malignant colon cells was assessed after exposure of the cells to electric, magnetic and electric-magnetic fields. Initial data showed an increase in clonogenicity indicating a stimulatory effect of electric and magnetic fields. Studies designed to replicate the initial data led to the conclusion that no firmly established effect could be demonstrated.

This study has generated a great deal of controversy and criticism, but also support. Becker observed that conclusions drawn from the section on cancer ignore important data that might have allowed opposing conclusions.⁵⁴ He states: "The report is not a scientifically valid document." In the same study, Savitz reported on childhood cancer and residential exposure to electric and magnetic fields, and decided that no conclusion could be reached from the information. However in a supplement to the contractor's original report he pointed to an association between low power magnetic fields and childhood cancer cases.⁵⁵⁻⁵⁷

Theoretical Considerations

Easterly has proposed that EM radiation may act as a weak promoter of carcinogenesis.⁵⁸ In his review he examines data suggesting that magnetic fields may be modifiers of mitotic index, of development rates and sizes, and of tissue and cellular respiration. Modification of self-physiology including turnover rates may then be a proliferative stimulus. As Easterly points out, although neither 0 nor 60 Hz magnetic fields interact with biologic tissue in the same manner as microwaves, similar biologic effects may occur for both, with 60 Hz being somewhat more prominent. A further theoretical model of the interaction of EMR and cancer has been provided by Stevens.⁵⁹ He has proposed that effects of EMR on the pineal gland and subsequent changes in melatonin-estrogen-prolactin may increase breast cancer risk, adding that this may have no true bearing on human breast cancer risk. Wertheimer and Leeper, after analysis of their data, also suggested, that there is a distinct pattern of latency consistent with tumor promotion.²⁵ Lin has also suggested that their data support the theory that non-ionizing radiation is a tumor promoter.²⁸ Finally, Balcer-Kubizek has concluded

that their animal data are consistent with the view that microwaves induce latent transformational damage.

Summary

A number of problems become evident when we attempt to assess the data in this review. We must first acknowledge the fact that EM radiation, as opposed to some chemical and physical pollutants which can be seen, tasted, or detected by odor, is in most situations not detected by human senses. This fact alone, however, does not prove or disprove the conjecture that EMR is a potential health hazard. The studies on the effects of EMR on cell systems, animals, and human subjects, report results which promote in some and reject in others the hypothesis that EMR in the ELF and microwave range is carcinogenic. Much of the criticism of the studies on human subjects centers around (1) quantifying exposure to EM Fields; (2) the epidemiologic-statistical methods used to gather, study, and interpret the data; and (3) lack of data studying co-carcinogens.

Although there is no convincing evidence that EMR is carcinogenic, the uncertainty, in addition to the ubiquity of EMR, makes study of its possible health effects and its carcinogenic potential an essential part of future medical and epidemiologic research.

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Erratum

In the December 1988 issue of *Rhode Island Medical Journal*, volume 71, number 12, the third heading under Recent Abstracts of Interest on page 490 was misspelled. It should read "Multifactorial Causes of Abnormal Liver Functions in AIDS" — Ed.

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NECROLOGY — 1988

Robert Gorfine, MD

Doctor Robert Gorfine, a general surgeon, died January 11, 1988 at the age of 69.

Doctor Gorfine graduated in 1944 from St Louis University Medical School. He was a medical officer in the Navy during World War II and the Korean War. Past Secretary and Past President of the Miriam Hospital Staff Association, Doctor Gorfine was also an associate professor at Brown University Medical School. He was a fellow of the American College of Surgeons and a diplomate of the American Board of Surgery.

Doctor Gorfine was the husband of Sylvia (Gross) Gorfine.

Kenneth G. Burton, MD

Doctor Kenneth G. Burton, orthopedic surgeon, died January 15, 1988 at the age of 82.

Doctor Burton was a 1931 graduate of Harvard Medical School. He served with the Army First Auxiliary Surgical Group in France and Germany during World War II with the rank of major. During the Campaign of the Normandy Invasion and the Battle of the Bulge, he was involved with the acute care of the wounded.

He served as chief of orthopedics and chief of the fracture service at Rhode Island Hospital from 1954 to 1965. His special interest areas were adult reconstructive surgery and child orthopedics and he was one of the first to design and insert a total elbow in 1965. Doctor Burton served as Chief Orthopedic Consultant to the Cripple Children's Division of the Rhode Island State Health Department from 1967 to 1985. Brown University honored Doctor Burton at its 1965 bicentennial celebration as one of six outstanding alumni. The Department of Orthopedic Surgery at Rhode Island Hospital established the Annual Kenneth G. Burton Lectureship in 1980. In 1986 Doctor Burton received the W.W. Keen Distinguished Service Award from the Brown University Medical Association for distinguished service and deep commitment to the medical community and Brown University.

Doctor Burton was the husband of the late Edith (Vayro) Burton.

William F. Maher Jr., MD

Doctor William F. Maher, Jr., surgeon, died January 23, 1988 at the age of 68.

Doctor Maher graduated from Georgetown University Medical School in 1944. He was on the staff of St Joseph and Roger Williams General Hospitals and a member of the Providence Medical and Rhode Island Medical Society. Doctor Maher was an international fellow of the College of Surgeons.

Doctor Maher was the husband of Stella A. (Finn) Maher.

Joseph B. May, MD

Doctor Joseph B. May, pediatrician, died January 28, 1988 at the age of 50.

Doctor May graduated in 1963 from Bowman Gray School of Medicine at Wake Forest College. Certified in 1975 through the American Board of Pediatrics, Doctor May specialized in developmental pediatrics, chronic illness in children, mental retardation, genetics and metabolic disease in children. He was appointed acting director of the Child Development Center at Rhode Island Hospital in 1975, Associate Physician of Pediatrics at Rhode Island Hospital in 1973, and Clinical Instructor of Pediatrics at Brown University in 1973.

Doctor May was the husband of Therese (Renquin) May, RN.

Katherine K. Cutts, MD

Doctor Katherine K. Cutts, a physician on the staffs of Rhode Island and Emma Pendleton Bradley Hospitals until her retirement in 1945, died February 9, 1988 at the age of 77.

Doctor Cutts was a 1936 graduate of Johns Hopkins University Medical School. She was a past president of Children's Friend and Service and was a founder of the Home Health Aide of Rhode Island Inc.

Doctor Cutts was the wife of Morgan Cutts, MD.

C. Thomas Angelone, MD

Doctor C. Thomas Angelone, general practi-

tioner, died February 14, 1988 at the age of 79.

Doctor Angelone attended St Louis University Medical School and pursued graduate studies at the Royal University in Rome, Italy. He was a member of the Rhode Island Medical Society. Doctor Angelone practiced medicine in Cranston for 45 years before his retirement in 1980.

Doctor Angelone was the husband of Barbara (Carlisle) Angelone.

Attilio L. Manganaro, MD

Doctor Attilio L. Manganaro, a South County physician, died March 9, 1988 at the age of 81.

Doctor Manganaro was a 1933 graduate of Georgetown University Medical School. He was chief of anesthesiology at South County Hospital for several years and also served as secretary-treasurer of the medical staff. A former Narragansett police surgeon during the 1950s, Doctor Manganaro also served as the South Kingstown High School football team doctor. He was a member of the Washington County Medical Society, the Rhode Island Medical Society and the American Medical Association.

Doctor Manganaro was the husband of Doris M. (Biggio) Manganaro.

William E. McKenney, Jr., MD

Doctor William E. McKenney, Jr., medical director at Kent County Memorial Hospital from 1982 until 1987, died March 19, 1988 at the age of 62.

Doctor McKenney graduated from Georgetown University Medical School in 1953. In private practice until 1981, Doctor McKenney was a member of the Kent County Memorial Hospital medical staff since 1955, former chief of the hospital's department of medicine and director of personnel health, as well as medical director at the Greenwood House Nursing Home. While medical director at Kent County, he was instrumental in development of the hospital's quality insurance program. Doctor McKenney was a member of the Kent County Medical Society, the Rhode Island Medical Society and the American Medical Association.

Doctor McKenney was the husband of Mary Elizabeth (Holton) McKenney.

Robert L. Curran, MD

Doctor Robert L. Curran, a specialist in cardiology and internal medicine, died July 25, 1988 at the age of 57.

Doctor Curran was a 1957 graduate of Tufts University Medical School. He was on the medical staffs of Miriam and Rhode Island Hospitals and was a consultant at Women and Infants Hospital. Doctor Curran was a member of the Providence Medical Association, the Rhode Island Medical Society and the American Medical Association. He was past president of the Rhode Island Society of Internal Medicine and a fellow of the American College of Cardiology and the American College of Physicians.

Doctor Curran was the husband of Betty (Brier) Curran.

John J. Cunningham, MD

Doctor John J. Cunningham, a physician practicing for 35 years, died August 17 at the age of 64.

Doctor Cunningham graduated from Tufts University medical school. He was an associate professor in the biomedical department at Brown University and founder and associate chairman of family medicine at Brown University/Memorial Hospital. A past president of the Pawtucket Medical Association and Rhode Island Medical Society, Doctor Cunningham represented the American Medical Association on the national residency review commission for family medicine. He had also been the Rhode Island delegate to the AMA for 12 years.

Doctor Cunningham was the husband of Biruta E. (Ciocys) Cunningham.

John F.W. Gilman, MD

Doctor John F.W. Gilman, general physician, died October 2 at the age of 69.

Doctor Gilman graduated from Harvard Medical School in 1944. He served in the Navy Medical Corps from 1946 to 1948. Doctor Gilman was on the staff of Rhode Island Hospital and its diabetes clinic for 30 years and served as staff physician for the Tockwotten Home, now the Bannister Nursing Care Center, the St Elizabeth Home and the Rhode Island School of Design. He was a member of the Rhode Island and Providence Medical Societies and the American Medical Association.

Doctor Gilman was the husband of Elizabeth (Erk) Gilman.

Max B. Fershtman, MD

Doctor Max B. Fershtman, a general practitioner, died October 6, 1988 at the age of 83.

Doctor Fershtman was a 1930 graduate of New York Medical College. He was a member of the Rhode Island Medical Society and the American Medical Association.

Doctor Fershtman was the husband of Frances (Weiner) Fershtman.

Linus A. Sheehan, MD

Doctor Linus A. Sheehan, an ophthalmologist, died November 25, 1988 at the age of 75.

Doctor Sheehan graduated in 1939 from Tufts Medical School. He served in the Army Medical Corps during World War II and was chief of ophthalmology at Valley Forge Hospital in Pennsylvania. Doctor Sheehan had a private practice in Providence and was on the staff of Rhode Island Hospital, St Joseph Hospital and Women & Infants Hospital. He was a member of the Rhode Island Medical Society.

Doctor Sheehan was the husband of Rose D. (Lodge) Sheehan.

Raphael A. Lussier, MD

Doctor Raphael A. Lussier, a practicing physician for more than 50 years, died December 9, 1988, at the age of 79.

Doctor Lussier received his medical degree from Jefferson Medical College and began practicing in Rhode Island in 1936. He was a member of Phi Alpha Sigma Medical Society and served for 40 years as anesthetist at Notre Dame Hospital.

Doctor Lussier was the husband of Jeanne (Blanchet) Lussier.

Charles L. Farrell, MD

Doctor Charles A. Farrell, a physician, dentist and pharmacist, died December 14, 1988 at the age of 91.

Doctor Farrell graduated from Tufts University Dental School in 1918 and received his medical degree from the university in 1923. He graduated with honors from the former Rhode Island College of Pharmacy in 1933.

Doctor Farrell was a member of the board of examiners in medicine for Rhode Island, the Pawtucket Medical Association, the Rhode Island Society of Industrial Physicians and Surgeons, the Association of American Physicians and Surgeons and the Conference of Presidents and Officers of State Medical Associations. He was also

a member of the Rhode Island and American Medical Association. He was the author of many books and papers on health insurance and medical economics.

Radiologic Case of the Month

Clinical History: An 81-year old male diabetic comes to the emergency room complaining of a sore swollen foot.



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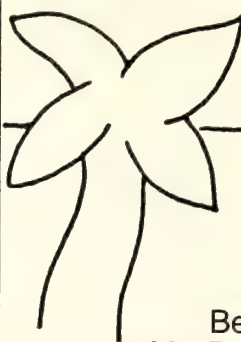
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NOTE: Lectures and courses are listed, when possible, by the date, sponsor, topic, speaker, and telephone number. Please call the contact number for additional information about the program.

BROWN UNIVERSITY PROGRAM IN MEDICINE (401) 863-3337

Second Annual Milton Hamolsky Visiting
Professorship
Speaker: Daniel D. Federman, MD
Date: February 15, 1989

Second Annual Irene Owens Memorial Lecture
Speaker: Barrie Cassileth, PhD
Date: April 5, 1989

Focus on Infection: 1989
Speakers: Edward L. Quinn, MD; Robert E.
Bryant, MD; Stephen C. Shimpff, MD;
C. Glenn Cobbs, MD; Edward H. Kass, MD;
John G. Bartlett, MD; Stephen H. Zinner, MD;
Roy T. Steigbigel, MD
Date: March 9, 1989

Third Annual Diabetes Symposium: Newport
1989
Speaker(s): TBA
Date: May 11, 1989

The Northeast Group on Medical Education
Speaker(s): TBA
Date: April 3-5, 1989

HIV Treatment and Management: 1990 and
Beyond
Speaker(s): TBA
Date: May 24, 1989

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Medicine/Family Medicine — Core Curriculum
Conference on Current Clinical Topics
Speaker(s): Multidisciplinary roster
Date: Mondays/Tuesdays/Wednesdays/Fridays
12:15 pm
Location: Sayles Conference Room #2 and 3
Cardiology Conference — Challenging
Cardiology Concepts
Speaker(s): Richard A. Carleton, MD, and
colleagues
Date: Every Tuesday at 8:00 am
Location: Wood 6 Conference Room

Hematology/Oncology Conference
Speaker(s): Manfred Steiner, MD, and
colleagues
Date: Every Tuesday (except last Tuesday of
month) at 8:00 am
Location: Immunology/Oncology Conference
Room
Tumor Board Conference
Speaker(s): Manfred Steiner, MD, and
colleagues
Date: Last Tuesday of each month at 7:30 am
Location: Physicians' Auditorium

Pediatric Grand Rounds

Speaker(s): Louise S. Kiessling, MD, and
colleagues

Date: Every Wednesday at 8:00 am

Location: Physicians' Auditorium

Medical Grand Rounds

Speaker(s): Distinguished guest speakers

Date: Every Wednesday at 10:00 am

Location: Physicians' Auditorium

Pulmonary Case Review

Speaker(s): Frederic G. Hoppin, MD, and
colleagues

Date: Every other Monday at 12:15 pm

Location: Sayles Conference Room #2 and 3

Infectious Disease Conference

Speaker(s): Kenneth Mayer, MD, and
colleagues

Date: Alternating Wednesdays at 12:15 pm

Location: Sayles Conference Room #2 and 3

Family Practice Grand Rounds

Speaker(s): Vincent R. Hunt, MD, and
colleagues

Date: Every Thursday at 12:15 pm

Location: Physicians' Auditorium

Surgical Grand Rounds

Speaker(s): Stephen J. Hoye, MD, and
colleagues

Date: Every Thursday at 8:00 am

Location: Physicians' Auditorium

Orthopedic Conference

Speaker(s): Richard G. Bertini, MD, and
colleagues

Date: Every Thursday at 8:00 am

Location: Sayles Conference Room #2

KENNEY DAY PROGRAM — SEMINAR —
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CASE CONFERENCES

January 12, 1989

Speaker(s): Sarah Zamari, MD — presenting
Duane Bishop, MD — moderating

January 26, 1989

Speaker(s): Sidney Heisler, MD — presenting
Leah Cullen, MD — moderating

February 9, 1989

Speaker(s): Lorin Mimless, MD — presenting
Matthew Edlund, MD — moderating

February 23, 1989

Speaker(s): Constanting Loures, MD —
presenting
Richard Goldberg, MD —
moderating

March 9, 1989

Speaker(s): John Melchionna, MD —
presenting
Eileen McNamara, MD —
moderating

March 23, 1989

Speaker(s): Aimee Schwartz, MD — presenting
Duane Bishop, MD — moderating

April 6, 1989

Speaker(s): Frank Jones, MD — presenting
Leah Cullen, MD — moderating

April 20, 1989

Speaker(s): Ronald Stewart, MD — presenting
Matthew Edlund, MD — moderating

May 4, 1989

Speaker(s): Christopher Joo, MD — presenting
Richard Goldberg, MD —
moderating

May 18, 1989

Speaker(s): Max Faintych, MD — presenting
Eileen McNamara, MD —
moderating

June 1, 1989

Speaker(s): Saul Martin, MD — presenting
Duane Bishop, MD — moderating

June 15, 1989

Speaker(s): Sarah Zamari, MD — presenting
Leah Cullen, MD — moderating

June 29, 1989

Speaker(s): Sidney Heisler, MD — presenting
Matthew Edlund, MD — moderating

RIMC/GENERAL HOSPITAL (401) 464-3456

Epidemiology and Neurology Lecture

Speaker: Stanley M. Aronson, MD — Professor
Emeritus, Brown

Date: January 9; February 13; March 13; April
10; May 8; June 12

Time/Location: 8:30 am; George C. Arnold
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Clinical Rounds (AIDS)

Speaker: Charles C.J. Carpenter, Jr., MD

Date/Time: Once monthly TBA — 8:15 am

Clinical Pathological Conference

Speaker(s): Invited speakers

Date/Time: Once monthly TBA — 10:30 am

Psychogeriatric Rounds

Speaker: Barry S. Fogel, MD, Associate
Director

Center for Gerontology and Health Care
Research, Brown

Date/Time: Once monthly TBA — 11:00 am

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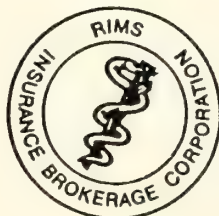
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Recent Abstracts of Interest

AIDS

No Serious Adverse Reactions to Live Virus Vaccine in HIV Infected Children

Immunocompromised patients are at increased risk for adverse reactions to live attenuated viral vaccines. Outpatient records of 319 patients infected with the HIV virus were reviewed to assess the frequency of untoward reactions after vaccination. Ninety-four percent of cases were due to perinatal transmission while six per cent were via transfusion. Immunization history was available in 221 of the 319 cases reviewed. Of these 221, 81 per cent had received at least one dose of oral polio vaccine and 70 percent had received at least one dose of a combination of measles, mumps and rubella. No serious adverse reactions were observed. In particular, post vaccination there were no instances of atypical or typical measles, paralytic poliomyelitis or aseptic meningitis.

The study is limited by its retrospective nature and small sample size. More subtle complications of vaccination may have been missed or erroneously attributed to other factors. In addition, the authors note that HIV infection in children is associated with a progressive defect in cell mediated immunity; thus the results of this study may be due in part to the timing of vaccine administration. Prospective studies will be needed to assess immunogenicity of childhood immunization in this context since poor antibody response in AIDS patients has been noted previously in other situations such as to influenza vaccine. This study adds to the data needed to help determine risks and benefits of immunization of children infected with the HIV virus. (McLaughlin M, Thomas P, Onorato I, Rubinstein A, Oleske J, Nicholis S, Krasinski K, Guigli P, Orenstein W: *Live Virus Vaccine in Human Immunodeficiency Virus Infected Children: A Retrospective Study Pediatrics* 82:229-233, 1988)

Multiple Rheumatic Complaints May Be Common in AIDS

One hundred and one consecutive patients with HIV infection were evaluated at an AIDS clinic. All completed a detailed questionnaire of rheumatic complaints. Seventy-five per cent were homosexual, eight per cent were IV drug abusers, ten per cent were both homosexual and drug abusers, while four per cent had received blood products. Seventy-two of 101 had rheumatic complaints, including 35 per cent who had experienced arthralgias, twelve per cent having arthritis, ten per cent with Reiter's syndrome and ten per cent with a painful articular syndrome, two per cent with psoriatic arthritis, two per cent with polymyositis and one per cent with vasculitis.

Arthralgias were intermittent in all but three of 35 patients, oligoarticular in 19, polyarticular in 12 and monoarticular in four. Knees and shoulders were most commonly involved. Arthritis was usually oligoarticular and involved particularly lower extremities. A particular, painful articular syndrome manifested by sharp, severe pain lasting less than 24 hours was seen in ten patients. No evidence of synovitis was present and in each case pain was described as debilitating and excruciating, requiring medication. Myalgias were present in ten patients and tended to be generalized. Six individuals had generalized muscle atrophy while two had polymyositis.

Immunodeficiency may potentiate arthritogenic organisms, while HIV may cause a direct musculoskeletal reaction or be associated with a reactive arthritis. Immune complexes may play a role in pathogenesis. This study suggests that in individuals at high risk for HIV infection, articular complaints should raise the possibility of AIDS-related disease. Rheumatic complaints are

common and diverse in HIV infection. (In *Berman A, Espinoza LR, Diaz JD, Aguilar JL, Rolando T, Vasey FB, Germain BF, Lockey RF: Rheumatic Manifestations of HIV Infection in Amer J Med 85:59-64, 1988*)

Interpretation of Cerebrospinal Fluid Findings May Be Difficult in HIV Infection

HIV is neurotropic and may be cultured from cerebrospinal fluid (CSF) in the absence of neurologic abnormalities; conversely a negative CSF culture does not exclude etiologic roles for HIV in a particular setting. Altered CSF inflammatory response to pathogens may be present as a consequence of the immunodeficiency of HIV. As immunosuppression progresses, inflammatory CSF changes decrease with protein elevation as the major abnormality.

In asymptomatic HIV seropositive individuals, a mild protein elevation and low-grade lymphocyte pleocytosis are relatively common. In patients with known HIV infection, CSF leukocyte counts greater than 100 per cubic ml suggests secondary infection. However, the absence of pleocytosis late in the disease does not include pathogens known to be associated with pleocytosis in immunocompetent individuals. Even in the absence of protein elevation or pleocytosis, clinical suspicion of meningeal disease warrants a search for appropriate pathogens in AIDS patients. HIV should be considered when acute or chronic meningitis is present in high risk individuals. (In *Hollander H: Cerebrospinal Fluid Normalities and Abnormalities in Individuals Infected with the Human Immunodeficiency Virus, J Infect Dis 158:855-858, 1988*)

Risk for Developing AIDS May Increase After the Third Year of Lymphadenopathy

This study is a prospective one of 75 HIV positive homosexual men with generalized lymphadenopathy for greater than three months. Twenty-two men (29 per cent) have developed AIDS 5-69 months after the onset of lymphadenopathy. The six year cumulative incidence of AIDS was 38 per cent. Twenty-six of the 75 patients had T-Helper Cell counts, less than 400 per cubic ml at enrollment; of these, 14 developed AIDS for a six-year cumulative incidence of 63 per cent in this subgroup; among the remaining 49 men, the incidence of AIDS was only 22 per cent. For the

entire group, the cumulative incidence of AIDS increased significantly after the third year of lymphadenopathy, suggesting that more patients in this cohort will subsequently develop AIDS. A declining T-Helper Cell count commonly preceded the onset of AIDS. This study adds to the information needed to determine prognosis in individual patients and suggests that the risk for development of AIDS increases after three years of infection. (In *Kaplan JE, Spira TJ, Fishbein DB, Bozeman LH, Pinsky PF, Schonberger LB: A Six Year Follow Up of HIV Infected Homosexual Men with Lymphadenopathy JAMA 260:2694-2697, 1988*)

Edited by Edward R. Feller, MD

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Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it, however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

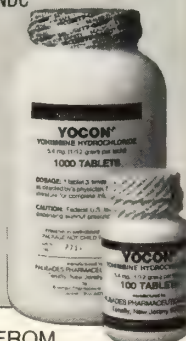
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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Answer to
Radiologic Case of the Month (from page 25)

Gas Gangrene of the Foot

Multiple bubbles of gas are present in the soft tissue along the fascial plane in the forefoot. Gas gangrene is a rapidly progressive severe infection of skeletal muscle due to Clostridia with *C. perfringens* involved in over 80 per cent of cases. This anaerobic infection occurs after muscle injury and subsequent contamination with soil or other substances containing Clostridial organisms. The clinical setting may be traumatic injury, postoperative infection such as in biliary or intestinal procedures, minor trauma to an extremity, especially in individuals with vascular insufficiency and occasionally reported in the absence of a clear history of external trauma.

The incubation period may be as short as six hours but usually the development of Clostridial myonecrosis takes 2-3 days. The clinical course is commonly characterized by rapidly spreading crepitation and severe systemic toxicity after an initial short period of pain and swelling in an extremity. The differential diagnosis includes soft tissue infections due to other gas forming organisms. Non Clostridial crepitant cellulitis has been described due to *E. coli*, *Klebsiella*, streptococcal species as well as to other anaerobes.

The above case was contributed by the Department of Radiology at Memorial Hospital in Pawtucket, Rhode Island.

There must be a good reason why



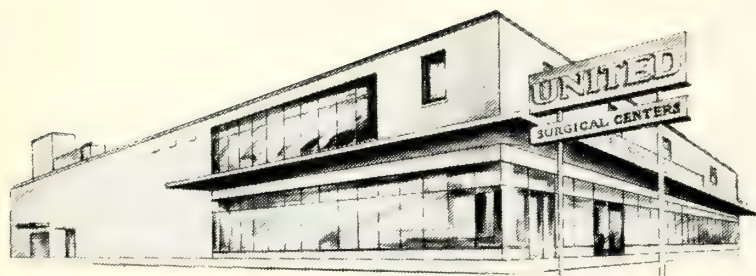
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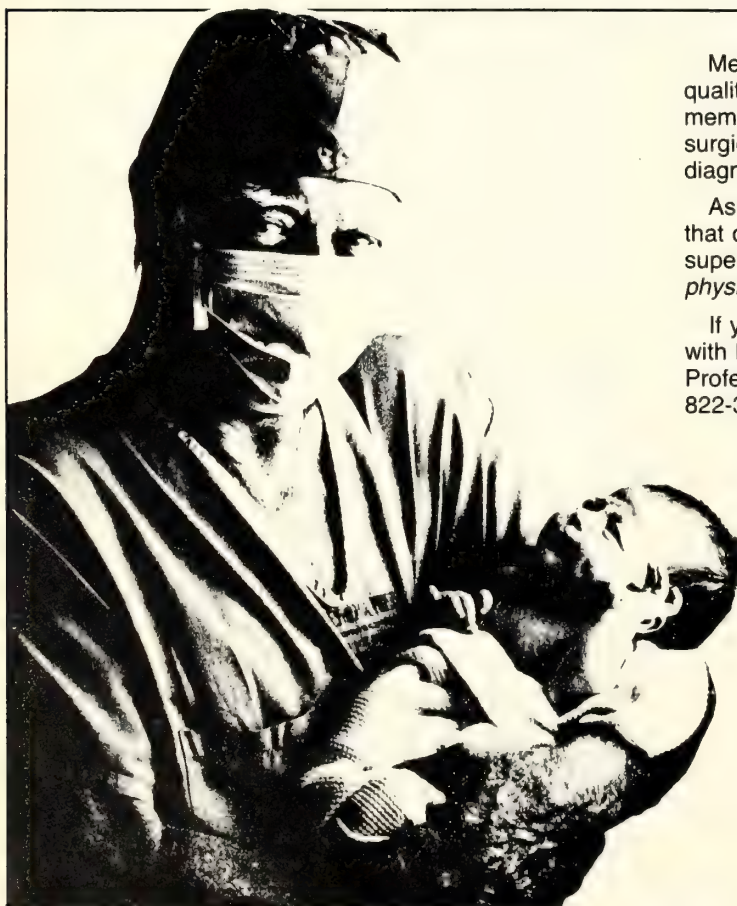


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Specifications: Manuscripts must be original typed copy (not all capitals) on 8½x11 inch firm typewriter paper, double-spaced (including the text, case reports, legends, tables, and references) with 1½ inch margins. Carbon copies will not be accepted. Subheadings must be inserted at reasonable intervals to break the typographic monotony of the text. Pages must be numbered consecutively. Italics and boldface print are never used except as subheadings.

Abbreviations: The *Journal* attempts to avoid the use of jargon and abbreviations. All abbreviations, especially of laboratory and diagnostic procedures, must be identified in the text.

Title page: All manuscripts must include a title page which details the following information: (1) a brief title; (2) the name of the author or authors with the highest academic degree (ie, MD, PhD); (3) a concise biographical description for each author which includes specialty, practice location, academic appointments, and primary hospital affiliation; (4) mailing address of principal author; and (5) office telephone number of principal author.

Illustrations: Authors are urged to use the services of professional illustrators and photographers. Drawings and charts should always be done in black ink on white paper. Clear, black and white glossy photographs should be submitted, and such illustrations numbered consecutively and their positions indicated in text. Original magnifications should be noted. Illustrations defaced by handwriting or excessive handling will not be accepted. The figure number, indication of the top, and the name of the author must be attached to the back of each illustration. Legends for illustrations should be type-written in a single list, with the numbers corresponding to those on photographs and drawings. Recognizable photographs of patients are to be masked and must carry with them written permission for publication.

Special arrangements must be made with the editors for excessive illustrations. Color plates are not acceptable.

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It is rarely desirable to include a complete review of the literature in the references. An alphabetized bibliography is to be used only when the listing is of books suggested for supplementary reading.



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INDICATIONS AND USAGE: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics, see **WARNINGS**.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS**, **WARNINGS**, and **OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS**); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
 2. Intravenous administration of 300 to 500 mEq of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.
 3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
 4. Use of exchange resins, hemodialysis, or peritoneal dialysis.
- In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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PERIPATETICS

Nominated by the American College of Emergency Physicians, **Dr Francis Sullivan**, an emergency room physician at Roger Williams General Hospital, was named Emergency Room Physician of the Year during Medical Services Week.

• • •

Director of Pathology at St. Joseph Hospital, **Dr Salvatore Allegra** recently returned from Italy where he lectured on Ultrastructural Pathology at the University of Ancona. The program was sponsored by the G. Cardinali Foundation and by the State Health Department.

• • •

The Department of Surgery at Landmark Medical Center recently honored three physicians for their service as Department Directors. They are **Dr Ramon D. Llamas** and **Dr Frank M. Detorie**, Department of Surgery — Fogarty Unit, and **Dr Francis L. Scarpaci**, Department of Surgery — Woonsocket Unit.

• • •

The American Thyroid Association elected **Dr Ivor M. D. Jackson** to the Board of Directors at their 63rd Annual Meeting held in Montreal, Canada. **Dr Jackson** is Physician-in-Charge with the Division of Endocrinology at Rhode Island Hospital, and Professor of Medicine and Director of the Division of Endocrinology at Brown University.

• • •

Dr Kathleen A. Cassin, an obstetrician/gynecologist in South Kingstown, has recently joined the Associate Medical Staff at South County Hospital.

• • •

Kent County Memorial Hospital has recently appointed the following physicians to its medical

staff: **Dr Stephen Bailey**, emergency medical physician; **Dr Ralph DiGiacomo**, rheumatologist; **Dr Daniel Harrop**, psychiatrist; and **Dr Tesie Rallos**, pulmonary medicine.

• • •

At a recent meeting of the American College of Physicians, **Dr Edward G. Feller**, gastroenterologist, presented results of a collaborative study with **Dr Albert Lin** on cancer of the pancreas.

• • •

Notre Dame Hospital has announced the following recent appointments: **Dr Gilbert J. Altongy**, Chief of Medicine; **Dr Eugene E. Healey**, Chief of Surgery; **Dr Khalil Shekarchi**, President of the Medical Staff; **Dr Fredy P. Roland**, Vice President of the Medical Staff; **Dr Earle Travis**, Secretary/Treasurer of the Medical Staff; **Dr Suhdong Hahn**, Member-at-Large of the Medical Staff; and **Dr Ibrahim Sabbagh**, Member-at-Large.

• • •

The National Heart, Lung and Blood Institution recently honored **Dr Frederic G. Hoppin, Jr**, Chief of Pulmonary Medicine at Memorial Hospital, with a Merit Award.

• • •

Dr Larry Culpepper, director of research and evaluation in the Family Medicine Department at Memorial Hospital, has been named president-elect of the North American Primary Care Research Group.

• • •

The Memorial Hospital has recently appointed **Dr David G. Kern** Chief of General Internal Medicine and Director of the Occupational Health Services.

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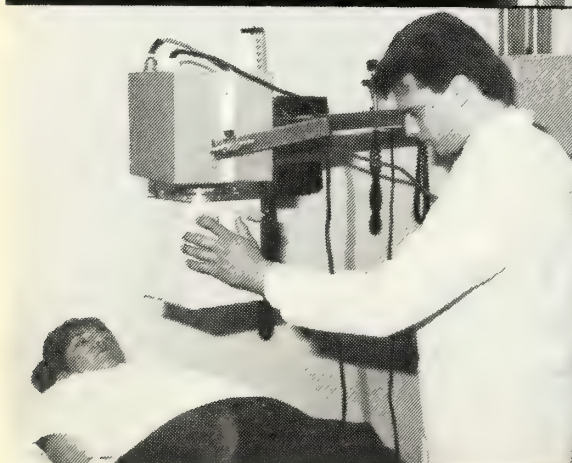
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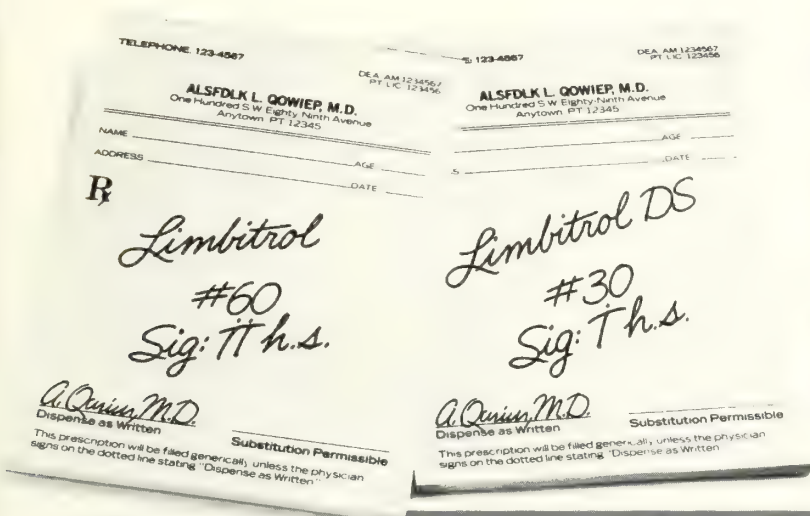
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References: 1. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 2. Feighner VP, et al: *Psychopharmacology* 61:217-225, Mar 22, 1979.

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Tranquilizer—Antidepressant

Before prescribing, please consult complete product information, a summary of which follows:

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants; concomitant use with MAOIs or within 14 days of monoamine oxidase inhibitors (then initiate cautiously, gradually increasing dosage until optimal response is achieved); during acute recovery phase following myocardial infarction.

Warnings: Use with caution in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur when used with anticholinergics. Closely supervise cardiovascular patients. Arrhythmias, sinus tachycardia, prolongation of conduction time, myocardial infarction and stroke reported with tricyclic antidepressants, especially in high doses. Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations. Consider possibility of pregnancy when instituting therapy.

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: Use cautiously in patients with a history of seizures, in hyperthyroid patients, those on thyroid medication, patients with impaired renal or hepatic function. Because of suicidal ideation in depressed patients, do not permit easy access to large quantities of drug. Periodic liver function tests and blood counts recommended during prolonged treatment. Amitriptyline may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady-state concentrations of the tricyclic drugs. Use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Should not be taken during the nursing period or by children under 12. In elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.

Adverse Reactions: Most frequent: drowsiness, dry mouth, constipation, blurred vision, dizziness, bloating. Less frequent: vivid dreams, impotence, tremor, confusion, nasal congestion. Rare: granulocytopenia, jaundice, hepatic dysfunction. Others: many symptoms associated with depression including anorexia, fatigue, weakness, restlessness, lethargy.

Adverse reactions not reported with Limbitrol but reported with one or both components or closely related drugs: **Cardiovascular:** Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke. **Psychiatric:** Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania, increased or decreased libido. **Neurologic:** Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns. **Anticholinergic:** Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract. **Allergic:** Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus. **Hematologic:** Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia. **Gastrointestinal:** Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue. **Endocrine:** Testicular swelling, gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion. **Other:** Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. Withdrawal symptoms also reported with abrupt amitriptyline discontinuation. Therefore, after extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

Overdosage: Immediately hospitalize patient. Treat symptomatically and supportively. I.V. administration of 1 to 3 mg physostigmine salicylate may reverse symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

How Supplied: Double strength (DS) Tablets, white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and Tablets, blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50.



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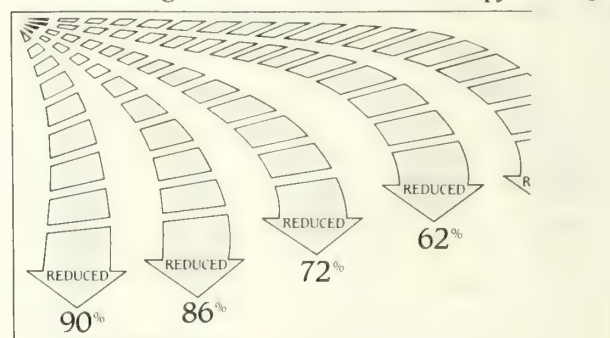
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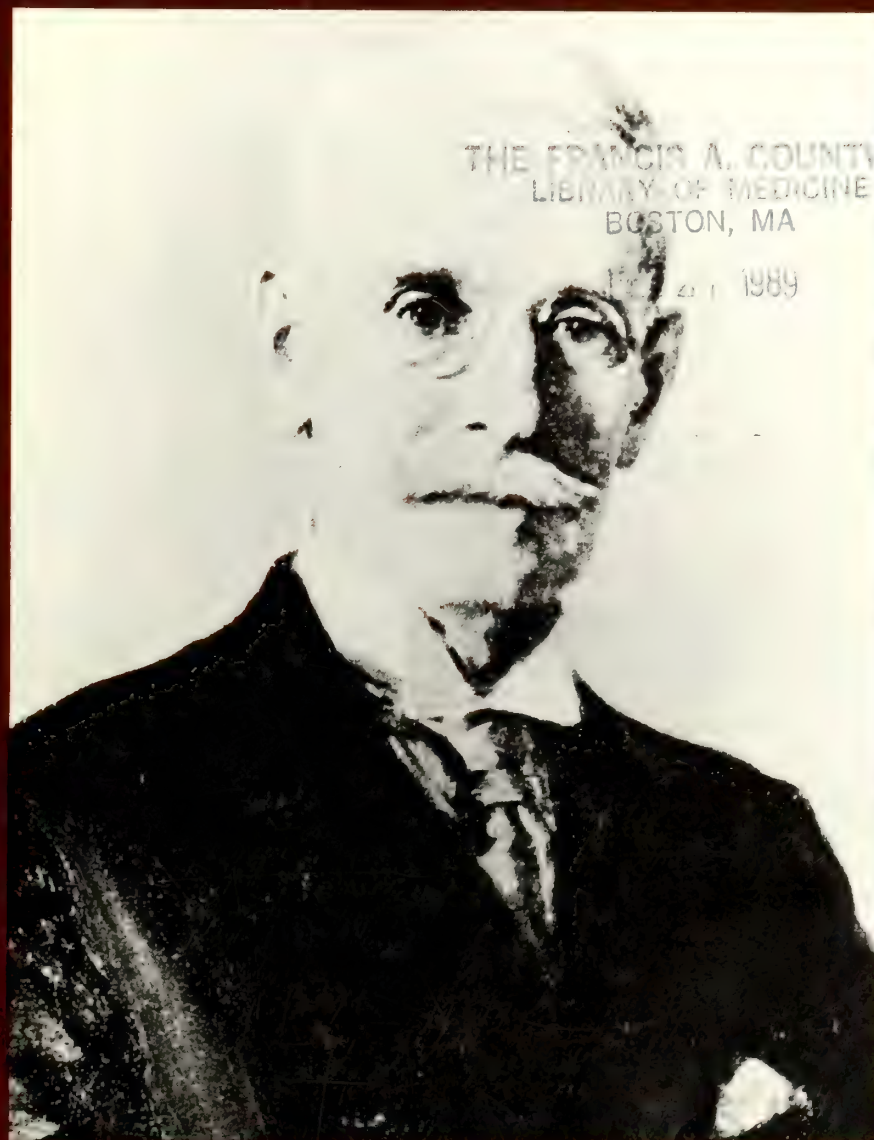


RHODE ISLAND MEDICAL JOURNAL



February 1989

Volume 72, Number 2



Charles V. Chapin, MD, 1856-1941

*Presentations
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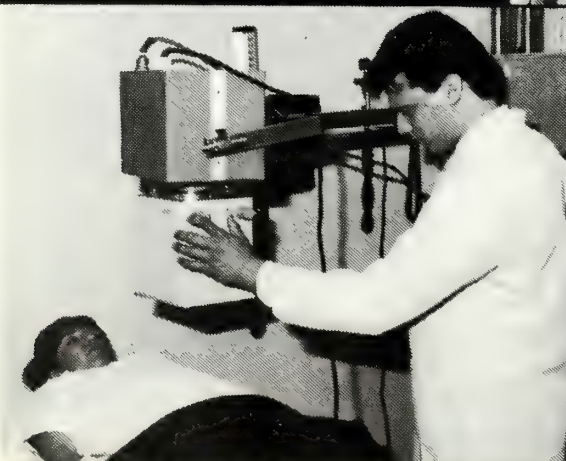
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Public Health

Cover: Photo of Charles V. Chapin, MD (1856-1941). The papers read at the 44th Chapin Oration on October 13, 1988 are published in this issue of the *Rhode Island Medical Journal*.

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moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made.

- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis

- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Ceclor penetrates mother's milk. Exercise caution in prescribing for these patients.

Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include:

- Gastrointestinal (mostly diarrhea) 2.5%
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] and toxic epidermal necrolysis or the above skin manifestations accompanied by arthritis/arthritis, and frequently, fever). 1.5%, usually subside within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Ceclor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonía, dizziness, and somnolence have been reported
- Other: eosinophilia, 2%, genital pruritus or vaginitis, less than 1%, and, rarely, thrombocytopenia

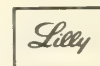
Abnormalities in laboratory results of uncertain etiology

- Slight elevations in hepatic enzymes
- Transient fluctuations in leukocyte count (especially in infants and children)
- Abnormal urinalysis, elevations in BUN or serum creatinine
- Positive direct Coombs' test
- False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clintest[®] tablets but not with Tes-Tape[®] (glucose enzymatic test strip, Lilly).

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GUEST EDITORIAL

The Nursing Shortage: A Professional's Viewpoint

It is certain that the nursing shortage is one of the most serious concerns in health care. A number of factors have led to this crisis. Many authors believe that the poor image and low salary of the nurse is the major culprit. No doubt, these conditions contribute to the difficulty in attracting new members to the profession. However, they are reflective of a deeper, more pervasive problem. This writer believes that a health-care system that devalues the caring component of nursing practice is the prime reason for the shortage. This caring aspect of nursing is focused on the unique nurse-patient relationship and the responsibility of the nurse to be an advocate for the patient within our complex health-care system. It is the nurse who anticipates and supports the needs of the patient. It is the nurse who promotes the patient's confidence in his ability to regain and maintain health. No other health-care group can claim such a comprehensive advocacy role. Registered nurses by mandate of their license are held accountable to the patient for their services — not to the physician, or to the institution. Nurses take this responsibility seriously, so seriously that some have chosen to leave the profession because they believe that they can no longer fulfill this caring role.

Nursing throughout its history has been at the forefront in the effort to improve patient care. Florence Nightingale was the first of many to fight for improved standards and conditions for patient care. Nurses view quality of nursing services and caring as synonymous. One simply cannot exist without the other. Today's focus on the

"bottom line" of health-care costs creates significant challenges for nurses in their efforts to provide health care. Care, as embodied in the nurse-patient relationship, is not easily discernable or measurable to the observer and as such has great potential to be undervalued or overlooked. However, if one asks a patient about the value of a nurse, the patient is sure to affirm need for their relationship. Quality nursing care is not just a series of tasks performed "as ordered by the physician." Quality nursing care embodies the use of nursing knowledge for the promotion of health. It complements medical care — it is not a component of medical care.

Nurses have long appreciated their complementary role in medical care. This has been demonstrated by the profession's willingness to work collaboratively with medicine in the health-care arena. Joint membership on a variety of commissions testifies to this. One would think that medicine would have a clearer picture of nursing due to the close relationship. Unfortunately, the opposite has occurred. Instead of embracing the American Nurses Association (ANA) and the National League of Nurses (NLN) proposals for alleviating the nursing shortage, the American Medical Association (AMA) has chosen to develop a substandard bedside caregiver.

The proposal for the Registered Care Technologist (RCT) as a bedside "physician extender" is an inferior alternative to the nurse. The RCT would be minimally trained, technically focused, and responsible for implementing physician orders at the bedside. This means that bedside pa-

tient care would be controlled by physicians, and the nurse's access to the patient would be jeopardized. Nurses currently implement the medical plan of care at the bedside. Often this is done in a cooperative and efficient manner. The RCT proposal would hamper and ultimately fragment the delivery of health-care services to patients. Surely, this will lead to an increase in morbidity and its concomitant health-care cost. Tasks such as the bed bath are used by nurses to achieve a number of goals, both nursing and medical. Washing of the patient, for example, is often the least important part of such a procedure. Observations on skin condition, response to medication, general health, and coping mechanisms are made, and teaching opportunities are taken advantage of during this "simple" procedure. The education and expertise of the nurse provide the ability to discover and alleviate many potential problems that would have significant impact on the patient's recovery. This expertise cannot be imparted through a minimal, technical training period that is developed and taught by physicians.

As long as nursing services are viewed as secondary to medical services, a shortage of educated and intelligent nurses will persist. The health-care system must recognize that nurses are the best coordinators and providers of bedside patient care. Nursing expertise must be appropriately utilized. Assistants in bedside care will be necessary. However, the nature, scope, education, and control of such assistants must remain with nursing. Nursing has excelled in caring for and about patients. It is time that nurses are recognized for this work. The very first step in demonstrating this recognition is the abandonment of the RCT proposal and the embracing of professional nursing's solution to the nursing shortage.

Christina Bond Sokoloff, RN, BS
Per Diem Staff member, Visiting Nurse Service
of Woonsocket, Rhode Island

This guest editorial is a practicing nurse's response to an AMA Board of Trustees report dealing with the nursing shortage that appeared in the June 1988 issue of the Journal. None of the recommendations presented in that report dealt with the AMA's Registered Care Technologists proposal.

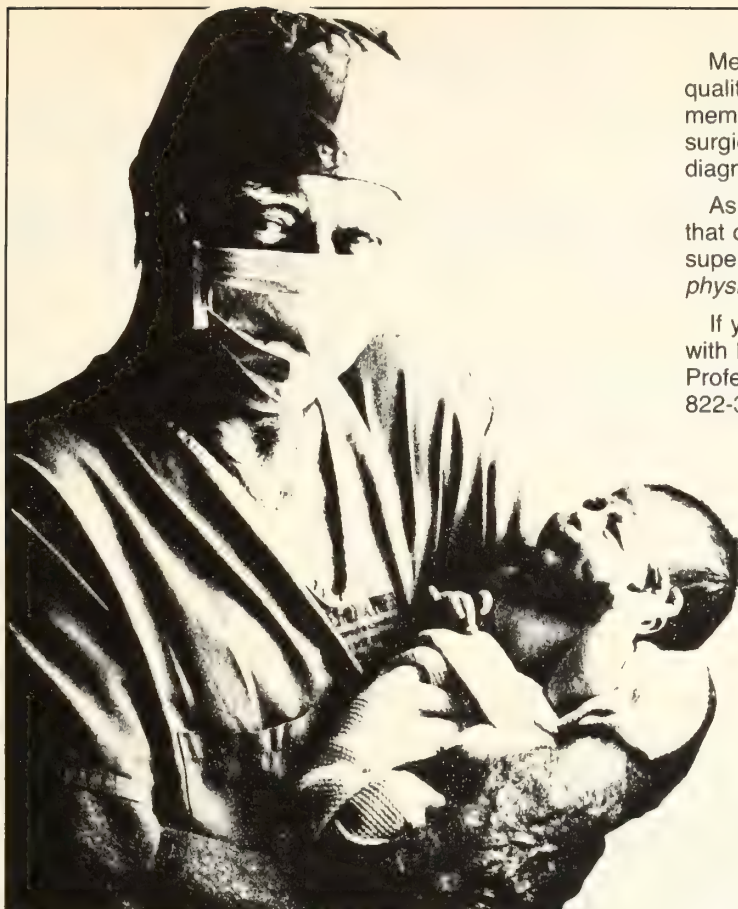
The AMA House of Delegates at its recent Interim Meeting in December 1988 passed the following resolutions bearing on the Registered Care Technologist proposal and the shortage of bedside care providers in general:

- *That the AMA continue to seek solutions to the problem of the shortage of bedside care givers, in addition to the Registered Care Technologists Program.*
- *That the American Medical Association, recognizing the concerns of our partners in health care, the nursing profession, work together with the American Nurses' Association and other nursing organizations to address the nursing shortage, and to continue to seek innovative ways to alleviate the acute shortage of bedside care providers, and that the Board of Trustees report to the House of Delegates at the Annual Meeting in 1989.*

A representative of the Rhode Island Medical Society has been an active participant on the Rhode Island Department of Health's Nursing Shortage Task Force.

Errata

In the December 1988 issue of the *Rhode Island Medical Journal*, volume 71, number 12, copy was inadvertently misplaced in Dr. Hyland's paper on Lyme Disease. On page 481, right hand column, the paragraph reading "Mowing the vegetation . . ." should be placed directly above the paragraph reading "2. Chemical Control . . ." Additionally, Dr. Jost's paper on Lyme Disease listed an incorrect dosage figure. On page 472, left hand column, the paragraph reading "1). Arthritis . . .," line 12 should read "doxycycline 100 mg by mouth twice daily. . . ." Ed.



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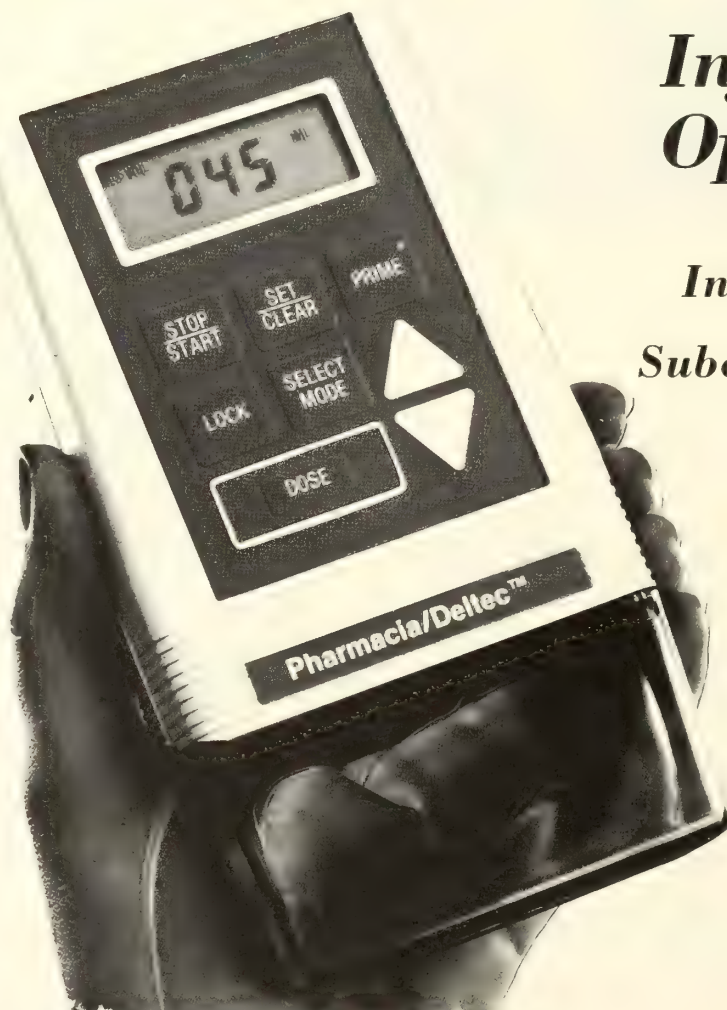


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DHHS Office of Inspector General: An Overview*

The Low Detection Rate of Sanctionable Incidents Argues Against Federal Surveillance Process Being Onerous or Intrusive

David Hsia, JD, MD, MPH

In 1976, Congress created the Office of Inspector General (OIG) at the then Department of Health, Education, and Welfare in response to repeated abuses of government programs.¹ Recapitulating high school civics, the federal government has three branches: legislative, executive, and judicial. The executive branch consists principally of the cabinet departments and independent agencies.

The current Department of Health and Human Services (DHHS) is the second largest of the cabinet departments with a Fiscal Year (FY) 1987 budget of approximately \$150 billion in programs and \$230 billion in Social Security (transfer) payments, nine per cent of the Gross National Product. It has five operating divisions (Public Health Service, Health Care Financing Administration, Social Security Administration,

Family Support Administration, Office of Human Development Services) and nine staff divisions (public relations, legislation, personnel, general counsel, civil rights, administration, and others). The OIG is one of the staff divisions.

The OIG has the statutory mission of promoting economy and efficiency in the department's programs and operations by preventing and detecting waste, fraud, and abuse.² In FY 1987, for example, the OIG recovered \$5.4 billion in fines, savings, restitutions, and settlements.³ This works out to about \$75 recovered for every dollar in the \$70 million budget of the OIG. Over five billion dollars sounds like a lot of money recouped, until divided into the department's budget: The recoveries by OIG amount to only 1.5 per cent of department spending during the same fiscal year.

Moving down the table of organization, the OIG has three operating components and an administrative component. The components differ in their activities, training required of prospective employees, and organizational culture.

The Office of Audit principally checks the books of other parts of the department, their contractors, and their grant recipients. These activities include auditing the DHHS computer systems, checking the overhead charges at universities, and reviewing the management of DHHS activities. Its employees are mainly accountants by training. Audit consumes over half of the budget and personnel of OIG.

David Hsia, JD, MD, MPH, is a Medical Officer with the Office of Inspector General, US Department of Health and Human Services in Washington, DC.

Doctor Hsia was awarded the Charles V. Chapin Medal at the 44th Charles V. Chapin Oration at Rhode Island Hospital, October 13, 1988.

* Office of Inspector General, US Department of Health and Human Services (DHHS), 330 Independence Avenue, SW, Washington, DC 20201. The views expressed in this paper do not represent the policies of any US government agency.

Table 1. Office of Inspector General functions (FY 1987)

OFFICES	Audit	Investigation	Analysis & Inspection
STAFF	630	416	130
BACKGROUND	Accountants	Investigators	Analysts-consultants
SAVINGS	\$4,668 million	\$75 million	\$647 million
ACTIVITIES	3100 audits	2800 investigations 1175 convictions 440 sanctions	100 inspections

The Office of Investigation looks into allegations of fraud and crime pertaining to all DHHS programs. Its staff of professional criminal investigators graduate from the boot camp for federal police officers at Glynco, Georgia, which also trains US Marshals, Secret Service agents, Border Patrol officers, National Park Police, and sky marshals. The investigators of OIG spend most of their time investigating criminal, prohibited, or improper activities by DHHS employees, contractors, grantees, practitioners, and providers. In addition, they spend about five per cent of their resources preparing administrative cases for exclusion or civil monetary penalty. Only a fraction of these relate to health care. They have a full time medical officer attached who acts as a hearing examiner for sanction cases, and may obtain additional medical review from the Medical Office of the Social Security Administration and the Armed Forces Institute of Pathology. Investigation absorbs over one-third of the money and personnel of OIG.

The Office of Analysis and Inspection studies the general function of the DHHS programs to identify vulnerabilities and recommend policy changes. Its analysts mainly have college degrees with strong research skills. Its employees come from diverse backgrounds. In the private sector their role would be analogous to that of a consulting firm, minus the fancy business degrees and big salaries. Their recent health related studies include centralizing bypass surgery, credentialing physicians, and pricing intraocular lenses. Inspection receives less than 15 per cent of OIG resources.

The usual administrative, executive, and overhead functions make up the balance of the organization. Overall, the OIG employs around 1200 full-time employees (FTEs), most of whom are scattered around the country in local and regional offices.⁴ Each employee therefore recovers an average of \$4.5 million each year. About 80 per cent are auditors, investigators, analysts, or their supervisors.

Comparative Epidemiology of Quality Assurance Systems

The health care system has recently come under increasing pressure to account for the quality of its services.⁵ Financial scandals, consumer activism, and escalating costs have all contributed to the public's demand for increased quality review in hospitals. This pressure has triggered an academic debate about the nature and measurement of quality in medicine. It has also produced multiple, overlapping systems of quality review that seem to "look over the shoulder" of the practitioner.

This paper does not address the complex controversy over structure, process, and outcome, as well as other theoretical issues of quality control.⁶ Rather, it uses "quick and dirty" methods to describe existing quality surveillance mechanisms and to compare their effectiveness. At present most practitioners simultaneously fall under four different systems.

- Peer Review Organizations (PROs) for Medicare prospective payment, backed up by sanction authority from Office of Inspector General (OIG).
- Traditional hospital-based peer review.
- State medical boards (SMBs), responsible for the licensing and discipline of physicians.
- Malpractice litigation, an indirect form of quality assurance.

Comparing their effectiveness entails relating research from different sources. In any meta-analysis, the multiple studies vary in their objectives, period of study, sample design, methodology, analysis, assumptions, and other essentials. The reader therefore needs to be aware of their technical limitations when contrasting them. Conversely, refusing to accept available data because of their possible imperfections means doing nothing and therefore having no information from which to make policy decisions.

Peer Review Organizations

In 1982 Congress established the PROs to replace the discredited Professional Standards Review Organizations.⁷ Among other things, the PROs examine a sample of Medicare hospital discharges to determine:

- Whether the services are . . . medically necessary. . . .
- Whether the quality of services meets professionally recognized standards. . . .
- The completeness, adequacy and quality of hospital care provided, and
- The medical . . . appropriateness of hospital admissions and discharges. . . .

They also check the accuracy of the disease codes used to make the Diagnosis Related Groups (DRG) assignment and the adequacy of medical records. The Medicare carriers theoretically perform a similar function for Part B reimbursement of physicians, laboratories, and related services.

The PRO evaluation process starts with nurses (or sometimes medical records professionals) who "ride circuit" from hospital to hospital checking a sample of medical records for clinical problems. The contract of the PRO with the Health Care Financing Administration (HCFA) specifies in detail the method of sample selection.⁸ In addition to using their judgement and experience, six so-called "generic screens" guide their analysis of a sample of records:⁹

- Stability at discharge
- Death
- Unscheduled return to the operating room
- Nosocomial infection
- Trauma suffered while hospitalized
- Adequacy of discharge planning.

If the nurse flags a case, it goes to a physician for review. Specialists review specialty cases and expert consultation is available. If the reviewing physician (MD) confirms poor quality care, unnecessary services, or premature discharge the PRO sends written notice to the practitioner.

The subsequent PRO process varies slightly depending on the nature of the problem and the proposed PRO action.¹⁰ Upon allegation of a "substantial number of substantial" instances of poor quality, the physician has 20 days to request a meeting or submit explanatory information. The PRO staff reviews the additional material and determines whether a violation of professional standards has occurred. If affirmed, it generally suggests a corrective action plan. Corrective actions may include discussions with PRO officials, increased volume of review, pre-admission review, further medical education, additional local supervision (eg, when performing certain operations or procedures), or formal penalties.

The physician under review may either accept or refuse the corrective plan. In the latter case, the physician receives a second notice and an additional 30 days to submit further information. Successive appeals may go to a panel of physicians and then to the PRO board. Only at the conclusion of these multiple opportunities to be heard and failure to resolve the case may the PRO refer it for sanction. The referral triggers a further opportunity to submit supplementary materials to the OIG. For an alleged "gross and flagrant" violation, the subject physician receives only one 30-day notice and may be directly subject to sanction without a corrective action plan.

What results have the PROs achieved? The National DRG Validation Study of medical records

Table 2. Epidemiology of PRO review

		Actual problem		
		Yes	No	
Screened positive:	Yes	70 True positives	410 False positives	480
	No	499,430 False negatives	8,499,590 True negatives	8,999,520
		500,000	8,500,000	9,000,000
Sensitivity		$= \frac{70}{500,000} = 0.014\%$		
Specificity		$= \frac{8,499,590}{8,500,000} = 99.995\%$		
Predictive value of a positive test		$= \frac{70}{480} = 14.6\%$		

to determine that at least 5.5 per cent of discharges have poor quality of care that the PRO should have detected and sanctioned.¹¹ Applying this rate to the population of nine million prospective payment discharges for which Medicare paid in Fiscal Year (FY) 1987 implies an incidence of 500,000 cases of poor quality for the PROs to detect. The PROs claim to have reviewed 23.7 per cent of all discharges for this period, targeting their two million screenings so as to detect as many of the half million poor quality cases as possible.¹²

For the first 14 months of the second contract period of the PROs, they issued 545 first notices of possible quality violations, or approximately 480 positive screenings for FY 1987.¹³ In the first 2½ years of the prospective payment system, the 54 PROs referred a total of 151 cases to the OIG for sanction, or about 70 true positives in FY 1987.¹⁴ Dividing by the projected subpopulation of 500,000 actual poor quality cases gives a sensitivity of 0.014 per cent. Thus, the PROs detect one out of 7143 sanctionable cases. Dividing the true negatives by the 5.5 million actual good quality non-cases implies a specificity of 99.995 per cent. So the PRO process has a one in 20,000 chance of baselessly accusing a practitioner of poor quality. Dividing the frequency of true positives by those discharges initially screened as poor quality gives a predictive value of a positive test of 14.6 per cent. Thus, only one sanction notice out of seven results in a subsequent sanction referral to the OIG.

In FY 1987 the PROs cost Medicare about \$150 million¹⁵ annually, with their activities principally focusing on quality assurance and utilization review.¹⁶ Accordingly, the PROs received \$17 for each prospective payment discharge, \$75 per record actually screened, \$312,500 for each sanction notice issued, or \$2,142,857 per OIG referral, depending upon the preferred cost-effectiveness divisor. Where did the PRO money go? One partial answer may be the 16 per cent profit rate attained by the PROs, with seven PROs keeping more than 20 per cent of their budgets in profits.¹⁷

In addition to low sensitivity, the Medicare quality review process suffers from high inter-PRO variation. Some 30 per cent of PROs have never identified any sanctionable quality deficiencies.¹⁸ Only two PROs have identified more than ten such cases. The PROs cite the high political and financial cost of reviewing quality cases and conflicts between their educational and enforcement roles. Physicians criticize the PROs for

inconsistent interpretation of the standard of review ("professionally accepted standards")¹⁹ and difficulty balancing the physician's right to due process with the patient's right to quality medical care. Academic observers note the difficulties defining what constitutes quality in medical care and assuring consistency between reviewers.

OIG Sanction

Upon identifying poor quality care, the PRO refers the matter to the OIG for possible sanction. The investigative responsibilities of the OIG include the detection of waste, fraud, and abuse in DHHS programs and development of sanction cases and civil monetary penalties. The vast majority of this activity focuses on 2,800 criminal and administrative proceedings of the OIG in FY 1987, not on sanctions.²⁰

Upon receiving a PRO case, the OIG gives the subject 30 days to submit additional material.²¹ The OIG staff reviews the PRO materials and recommendations and any materials submitted by the practitioner. An analyst determines compliance with statutory and regulatory requirements. Several physicians review the medical basis. An attorney reviews the legal sufficiency. The OIG may either sustain the PRO recommendation, alter the recommendation, or reject the recommendation. The OIG has 120 days to complete its process, or by statute the sanction goes into effect automatically.

Upon OIG action, the provider or practitioner may appeal to an Administrative Law Judge (ALJ) for a *de novo* hearing. Each side presents evidence and witnesses, may be represented by counsel, and has the right of cross-examination. The written opinion of the ALJ may sustain, modify, or dismiss the sanction. Subsequent appeals go to the Departmental Appeals Council and then the federal court system. The exact process varies slightly depending upon whether the PRO proposes a civil monetary penalty or Medicare exclusion.²²

As noted above, the PROs issued approximately 480 notices of possible sanction in FY 1987. Of these, about 70 got to the OIG, the other incidents being satisfactorily explained to the PRO or foundering on procedural grounds. The OIG then accepted 25, but rejected 45 as medically or procedurally inadequate. Assuming the non-referred cases to have the same distribution of good and poor quality as the general Medicare population (94.5 per cent and 5.5 per cent respectively), implies the process correctly identified 52.1 per cent of poor quality cases (the sensitivity)

Table 3. Epidemiology of OIG sanction

		Actually sanctionable		
		Yes	No	
Screened positive:	Yes	25	45	70
	No	23	387	410
		48	432	480
Sensitivity = $\frac{25}{48} = 52.1\%$				
Specificity = $\frac{387}{432} = 89.6\%$				
Predictive value of a positive test = $\frac{25}{70} = 35.7\%$				

and 89.6 per cent of the good quality cases (the specificity). Some 35.7 per cent of referred cases actually underwent sanction (the predictive value of a positive test).

Thus, out of 500,000 sanctionable hospital incidents each year, the combined PRO-OIG process identified and sanctioned a total of 0.005 per cent. This rate results principally from the low sensitivity of the PRO screening process. It should reassure providers and practitioners that the process interferes little with clinical practice.

The OIG part of the sanction process costs about \$500,000 annually. Divided into the case load, the OIG has a cost effectiveness of about \$1,000 per PRO notice, \$7,000 per screening investigation, or \$20,000 per actual sanction. In addition to the previously described problems of inconsistent standards for medical review and the low volume of PRO referrals, the OIG part of the sanction process suffers from the resource-intensive nature of "making" a medical case (versus the more open-and-shut character of a theft case), limited OIG resources, and the prolonged appeal process.

Hospital Based Peer Review

Arguably, this traditional system of quality assurance provides true "peer review." Local physicians check each others' work to maintain the hospital's overall medical quality. The mutual candor necessary for such a system to function requires absolute confidentiality. In consequence, no figures exist for the rate or frequency of peer review, the findings of the process or the actions driven by those findings. Statistics on the cost of peer review do not exist either. Both topics warrant further inquiry, but offer no data for comparison purposes at present.

State Medical Boards

The state medical boards (SMB) have responsibility for the licensure and discipline of physicians, rather than for the direct quality of care rendered to patients by their licensees. However, these appropriate and necessary functions form an interesting parallel for epidemiological and cost comparisons.

About 20,000 new MDs seek licensing from one or more of the 50-plus state medical boards each year.²³ American-trained MDs present relatively few credentialing problems because the quantity and quality of their training can be independently verified.²⁴ Accordingly, the boards devote most of their licensing resources to the 8.0 per cent who are foreign national-foreign medical graduates and the 9.8 per cent that are US national-foreign medical graduates (in 1984). A number of scandals involving poor training, purchasing of foreign medical degrees, and cheating on the FLEX examination have challenged the limited resources of the state medical boards.

Turning from licensing to professional discipline, the state medical boards are responsible for the behavior of approximately 550,000 presently licensed MDs. Between 1982 and 1984 they increased their number of disciplinary actions from 953 to 1,381.²⁵ However, tier-1 actions involving revocation, probation, or suspension remained steady at about 600 annually throughout this period, a rate of 0.1 per cent of all MDs. Half the actions were for writing inappropriate narcotics prescriptions and one-quarter for personal impairment with drugs or alcohol. The remaining quarter included a variety of incidents such as improper personal behavior, non-medical criminal convictions, and reciprocity for medical discipline in another jurisdiction. Few actions pertain to poor quality of care. State medical boards cite the difficulty and expense of developing such cases.

Unfortunately, no data sources quantitate the effectiveness of the state medical boards in quality assurance. However, figures do exist for measuring physician impairment. Assessing impairment may not have the judgmental characteristics of assessing quality of care, but the SMB process would probably have the same magnitude of sensitivity, specificity, and predictive value of a positive test.

A recent meta-analysis of the multiple studies of drug and alcohol abuse among MDs suggests 1.2 per cent prevalence for physicians requiring institutional treatment or dying of addiction-related causes, basically the same rate as the pop-

Table 4. Epidemiology of SMB discipline for impairment

		Actual impairment		
		Yes	No	
Screened positive:	Yes	350	700-6,650	1,050-7,000
	No	6,250	536,750-542,700	543,000-548,950
		6,600	543,400	550,000
Sensitivity = $\frac{350}{6,600} = 5.3\%$				
Specificity = $\frac{536,750-542,000}{543,400} = 98.8-99.7\%$				
Predictive value of a positive test = $\frac{350}{1,050-7,000} = 5.0-33.3\%$				

ulation at large, controlling for social class.²⁶ This rate implies a subpopulation of about 6,600 impaired physicians (cases) warranting state-medical-board supervision. The 350 or so tier-1 and -2 actions for impairment therefore correctly detect 5.3 per cent of impaired physicians, the sensitivity.

Only anecdotal data exist about the rate of referrals to SMBs for impairment. These reports suggest that about one out of 3-20 referrals results in SMB action. Assuming therefore, a range of 1-7,000 SMB screenings implies correct rejection of 98.8-99.7 per cent of non-impaired physicians, the specificity; and 5.0-33.3 per cent as the predictive value of a positive test. Note that these calculations compare prevalence rates, rather than incidence rates, an unavoidable limitation of the data, absent estimates of the duration both of impairment and of being a physician.

The state medical boards depend principally on renewal fees to finance their disciplinary activities. Their combined \$50 million budget implies a cost effectiveness of less than \$100 annually per licensed physician, \$3-24,000 per screening, or \$143,000 per disciplinary action. This simplified calculation makes no deduction for the costs of licensing, because the applicants bear most such expenses and this revenue mainly accrues to the National Board of Medical Examiners.

As with the PROs, considerable variation exists from state to state. Some hardly discipline anyone, while others are fairly aggressive. The usual limitations on resources and the need to balance due process with public protection apply to the state medical boards. Current controversies include (1) the evidentiary role of malpractice litigation and (2) discipline for activities not pertaining to professional conduct.

Malpractice

The tort system has the objective of compensating victims of civil wrongs, not punishing wrongdoers or assuring quality medical care. However, legal scholars argue that financial liability deters careless behavior, such as poor quality professional services.²⁷ The judicial elements necessary for a malpractice case include negligence, causation of injury, and damages.²⁸ Theoretically, poor quality of care goes only to the element of negligence, whereas the size of the judgment depends upon the damage to the plaintiff. Critics charge that the personal appeal of the plaintiff and personality of the defendant confound any causal relationship between the merits of the case and its outcomes. Procedurally, the injury results in the filing of a suit, reply by the defendant, discovery via interrogatories and deposition, settlement or trial, judgment, possible appeal, and (if adverse) payment of damages.²⁹

In 1977 the California Medical Association conducted a survey of inpatient medical care and concluded that 4.65 per cent of hospitalized patients incur medically caused injuries.³⁰ Applying this rate to the 34 million hospital discharges in 1984 suggests that around 1.5 million incidents of malpractice occur annually.³¹ More recently, the US Government Accounting Office (GAO) projected that medical malpractice insurers received 73,472 claims in 1984.³² Of these, 31,887 lawsuits and settlements resulted in a payment. Eighty per cent of events occurred in the hospital, 13 per cent in the office, and 7 per cent elsewhere; while 8.6 suits occur annually per 100 physicians.³³

Cross-tabulating malpractice claims against actual malpractice suggests that 2.1 per cent of incidents correctly result in liability, the sensitivity, while the process correctly rejects 99.9 per cent

Table 5. Epidemiology of malpractice litigation

		Actual malpractice		
		Yes	No	
Malpractice claim:	Yes	31,887	41,855	73,472
	No	1,468,113	32,458,145	33,926,258
		1,500,000	32,500,000	34,000,000
Sensitivity = $\frac{31,887}{1,500,000} = 2.1\%$				
Specificity = $\frac{32,458,145}{32,500,000} = 99.9\%$				
Predictive value of a positive test = $\frac{31,887}{73,472} = 43.4\%$				

of non-malpractice, the specificity. Of malpractice actions filed 43.4 per cent produce a recovery, the predictive value of a positive test.

The latter study notes that malpractice defendants and insurers paid out \$2.6 billion in damages for the index year. They also incurred \$0.8 billion of investigation and defense costs; mainly lawyers' fees, but also some expert witnesses and investigators. The American Medical Association estimates that defensive medicine increases health care costs by \$15 billion annually. Even if accurate, the latter figure amounts to only 3.8 per cent of the \$391.1 billion spent on health care in 1984.³⁴ The \$3.4 billion in direct malpractice costs therefore constitutes less than one per cent of health-care expenditures, about the same as for businesses in the manufacturing sector.³⁵

This amount comes to \$100 per discharge, \$46,000 per claim, or \$107,000 per successful claim. One hundred dollars per discharge might seem like a lot to pay for malpractice. It could almost appear as a separate item on the hospital bill along with room charges or respiratory therapy. However, since the average 1984 hospital bill was over \$5000, it amounts to less than two per cent of charges.

The payment per successful claim conceals a very skewed distribution. It has a median of \$18,000, but an average of \$81,000, implying that a few recipients got most of the money and a lot of recipients got only a little money. Specifically, payments over \$250,000 comprise only nine per cent claims, but accounted for 61 per cent of the dollars. Broken out by specialty, general surgeons pay the largest number of claims, but obstetricians have the highest payment per successful claim.

Discussion

Comparing the epidemiology of these approaches to quality review: PRO screening has the highest type-1 error (or lowest effectiveness at detecting poor quality care), but the lowest type-2 error (or highest effectiveness at screening out good quality care).³⁶ It also has the lowest efficiency (positive screenings confirmed upon review). OIG review has the lowest type-1 error, highest type-2 error, and intermediate efficiency. Malpractice litigation has the highest efficiency, with nearly half of suits producing a recovery, high type-1 error, and low type-2 error. The state medical boards fall somewhere in between.

As measured by the sensitivity, the poor-quality discharge or physician has 0.02 per cent chance of being detected by the PRO, two per cent chance of winding up in a malpractice action, and 0.3-1.2 per cent chance of coming to the attention of the medical board. Deducting the specificity from one, the good-quality discharge or physician has even less to worry about, with a 0.005 per cent chance of being screened positive and then not being referred for sanction by the PROs, 0.3 per cent chance of being accused of impairment by the state medical board when not impaired, and 0.1 per cent chance of being unjustly sued for malpractice. Accordingly, despite the low absolute probability, the poor-quality discharges or physician has 4-21 times greater chance of becoming embroiled in proceedings related to quality assurance.

This epidemiology affects the cost effectiveness of quality assurance. The PROs have the lowest unit cost for screening, \$17 per discharge; but their low yield produces a very high cost per case. The OIG sanction process has the highest cost per population because of the latter's small size. The high sensitivity of the OIG and speci-

Table 6. Quality assurance epidemiology

	PROs	OIG	SMBs	Malpractice
POPULATION				
Total	9,000,000	480	550,000	34,000,000
Screened	2,000,000	480	2,100-14,000	?
Screened positive	480	70	?	73,472
True positive	70	25	350	31,887
EPIDEMIOLOGY (%)				
Sensitivity	0.014	52.1	5.3	2.1
Specificity	99.995	89.6	98.8-99.7	99.9
Predictive value of a positive test	14.6	35.7	5.0-33.3	43.4
COST (\$)				
Total (million)	150	0.5	50	3,400
Per population	17	1,042	91	100
Per screening	75	1,042	3,571-23,810	?
Per screened positive	312,500	7,143	?	46,276
Per true positive	2,142,857	20,000	142,857	106,627
SEPARATION OF CASES AND NON-CASES				
1-specificity (%)	0.005	10.4	0.3-1.2	0.1
sensitivity/(1-specificity)	4	5	4-18	21

ficity give it the lowest costs per screening and case. The state medical boards have high screening costs, but do well on other axes. Malpractice litigation has low case costs given its victim compensation component.

What does this mean to the practitioner? First, keep good medical records. High-quality workup and therapy without documentation could place the physician in a very difficult position under any of these systems, if something subsequently goes wrong.

Second, both the competent and incompetent practitioner have little chance of encountering any quality-assurance system. PRO detection of 0.014 per cent of sanctionable incidents argues against federal surveillance process being onerous or intrusive.

Third, if selected for PRO review there is no reason not to cooperate. Eighty-five per cent of PRO notices of proposed sanction do not result in OIG referral. Two-thirds of referrals are rejected. Statistically, the odds of exoneration are 19 out of 20 regardless of the actual quality of care.

Acknowledgements

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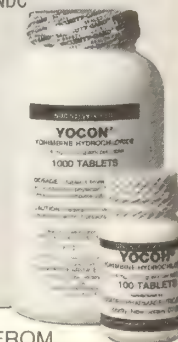
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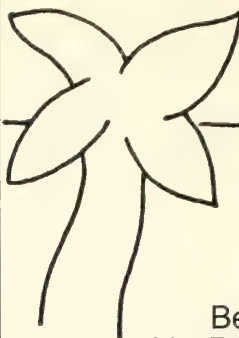
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Status of the Rhode Island Board of Medical Licensure and Discipline

The Public Must Be Educated that an Unfortunate Outcome Does Not Automatically Represent Substandard Care

Milton W. Hamolsky, MD

I am looking forward to the presentation by our Chapin Orator for 1988 on the overall global aspects — the macrocosm of regulation of the medical profession now swirling across this country. My task is to report briefly on the microcosm of Rhode Island's twenty-two-month-old Board of Medical Licensure and Discipline.

The first citation I could find concerning physician licensure in Rhode Island was in 1896 — consisting of the definitions of “a physician” and of the “practice of medicine,” which were then inserted into our general laws in 1923 and into the licensure act in public laws in 1927. In 1976, as one element of the response to the growing malpractice crises, a semi-autonomous Board of Medical Review was created with the authority to “investigate, review and monitor the professional conduct of physicians and to impose sanctions or other conditions on physicians found guilty of unprofessional conduct.”

Creation of New Board

Effective 1 January 1987 the legislature, seizing upon an exposé of serious unprofessional con-

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The following paper was read at the 44th Charles V. Chapin Oration at Rhode Island Hospital, October 13, 1988.

duct by one physician and — equally importantly — the prolonged failure of the medical profession to “do anything about it” created a new Board of Medical Licensure and Discipline, thus establishing a single body to deal with both licensure (initial and annual re-licensure) and the issues of professional disciplining. Among other changes the new Board is now responsible to the Director of Health and, therefore, to the executive branch of state government. In the new law there are increasing requirements for licensure and re-licensure, rigorous and sweeping statutory requirements for the composition of the Board, mandatory reporting to the Board of incidents or complaints or any diminution in hospital privileges, guidelines for investigation of complaints, expanding definitions of unprofessional conduct, definitions of the decision process, due process for the physician, increasing range of sanctions, subpoena power, immunity for those reporting to the Board and for various peer review groups as well as for members of the Board and its staff if acting in good faith and without malice, safeguard of confidentiality, and absolute requirements for the publication of any decisions of unprofessional conduct and any resultant sanctions. We are limited to judgments concerning MDs and DOs — not of hospitals as institutions.

Turning first to licensure, during the past year we have assumed the responsibility for licensure and annual relicensure of some twenty-seven hundred physicians, certification this year for the twenty-seven hundred physicians of the required sixty hours of continuing medical education over

the past three years, clarification of the inactive status of one hundred and fifty-two physicians and approximately five hundred limited licenses for interns, residents, and fellows.

Composition of Board and its Powers and Duties

By law the Board is composed of twelve members plus the Director of Health as chairman; four MDs (one of whom shall be a full-time medical school faculty member), two doctors of osteopathy, and six public members — one hospital administrator, one attorney with experience as plaintiff's counsel in medical malpractice matters, one at least sixty years of age, and three not associated with the medical field. Two MDs and one public member serve as a subcommittee of examiners for licensure in allopathic medicine; two DOs and one public member serve as the sub-committee of examiners for osteopathy. There are two investigative subcommittees each composed of two physicians and two public members. The staff consists of the chief administrative officer, a deputy assistant, five secretaries, two investigators, and legal counsel under contract. All activities of the Board are funded from annual physician and hospital fees, credited to a restricted receipt account, utilized only for the purposes of maintaining, managing, operating, and administering all matters of licensure and discipline. Each hospital pays an annual fee, in a fixed ratio to the MD fee, for each hospital bed it services.

The statutory powers and duties of the Board include the mandates to: establish rules, procedures, and regulations deemed necessary to carry out the requirements of the law, investigate all complaints and charges of unprofessional conduct and hold hearings to determine whether such charges are substantiated or not; direct the director of health to license duly qualified applicants; direct the director to revoke, suspend, or implement other disciplinary actions; and issue subpoenas, take or cause depositions to be taken, and summon and examine witnesses during any investigation, hearing, or proceeding conducted by the Board.

Procedures

The Board has evolved the following protocols: complaints or reports of disciplinary actions or claims filed or settled are received in writing from an individual, a hospital; another MD, medical association, medical society; health care facility;

Health Maintenance Organization (HMO); peer review board, medical service bureau; health insurance carrier; Peer Review Organization (PRO), and agency of federal, state, or local government, including the courts. If a hospital reports a diminution of staff privileges for any reason, the Board must be informed and then inform all health-care facilities, unless the decreased privileges are for purely administrative reasons.

All complaints or such reports are evaluated by the chief administrative officer and the deputy. If the complaint appears to be substantive, it is forwarded to the MD or DO involved for clarification and response in writing. The complaint and physician response are then forwarded to one of the investigative committees of four members for evaluation together with any hospital records, physician's records, relevant x-ray films, electrocardiograms (EKGs), laboratory results, and other relevant materials. The subcommittee may request any additional data from any source, including consultations from outside experts in the related field, and may invite the complainant, or the physician or both to an informal hearing. The Board is not confrontational, and we do not have the complainant and physician appear at the same time.

If the subcommittee concludes after due deliberation of all the relevant data that there is substantial cause for a recommendation of unprofessional conduct, according to one or more definitions detailed specifically in twenty-eight separate sections of the statute, our legal counsel is directed to prepare a consent order, detailing the findings of fact and proposed sanctions. The consent order is provided to the physician and his/her legal counsel, only after an interview with the physician. The physician or his/her legal counsel may request alterations of the consent order. These are then considered by the investigating committee. All proceedings of the investigative committee are kept strictly confidential.

Disposition of Cases

If the physician accepts and signs the consent order — and only if the physician signs — the formal vote of the subcommittee is then forwarded to the full Board with recommendations for a sanction. The range of sanctions is also detailed in the statute: formal reprimand; suspension, restriction, or revocation of licensure; period of probation; submission to care or counseling or treatment by a physician or program

acceptable to the Board; or participation in a program of continuing medical education, practice under direct supervision, and assessment of administrative costs. The substance of the case and the recommended sanction(s) are then presented to the remaining eight members (four physicians, four public members) who have been purposely kept without knowledge of any prior deliberations of the subcommittee. The pros and cons of the case are deliberated again by these eight members. This group may accept, modify, or reject the recommendation of the subcommittee or may ask for further investigations, outside consultations, or other information. If the Board finally votes a finding of unprofessional conduct, it directs the Director of Health to sign the consent order, which at that point becomes a matter of public record.

If the final vote of the full Board is no unprofessional conduct, all proceedings remain strictly confidential, and the only ones informed are the complainant, the physician, and his/her legal counsel. If the final vote is unprofessional conduct and is accepted by the physician, the consent order is published in the legal proceedings of the newspaper. The decision must also be distributed to health-care facilities of the state and must be reported to the Federation of State Medical Boards, the national organization of all state medical boards located in Texas.

If the physician or legal counsel does not in the first instance accept the consent order prepared upon the vote of the subcommittee, the Board's legal counsel prepares specification of charges for a formal hearing to be conducted by five of the eight untainted remaining members of the Board. The hearing committee will subpoena any witnesses, consultants, or others requested by the physician, and both sides are represented by legal counsel in the formal hearing. The investigative subcommittee does not participate in the hearing. A vote of four of the five members is necessary for a final decision of the hearing committee. The physician may then appeal the final judgment of the Board, the Director, or both, by filing a notice of appeal in accordance with the rules of civil procedure in the superior court within thirty days of the decision. The Director of Health, within twenty days of the notice of appeal, must transmit to the clerk of the superior court a transcript of the record together with a certified copy of the Board's written findings. Said appeal, considered an emergency matter, shall have precedence on the calendar and shall follow the procedures set forth

in the administrative procedures act, Chapter 35 of Title 42.

Experience of the Board

In the twenty-one months, from January 1, 1987 through September 30, 1988, two hundred and twenty-nine (229) cases have been considered and completed. Of these, one hundred and ninety-five (195) were closed as "no unprofessional conduct" and have remained confidential, unless the physician involved elected to announce the finding. In twenty-two (22) cases, the decision was unprofessional conduct (9.6 per cent). Of these twenty-two (22), ten (10) required surrender or revocation of license and twelve (12) involved a reprimand or other action concerning the scope of practice. Twelve (12) cases were placed in abeyance pending a request for re-licensure. By September 30, 1988 another thirty cases had been voted upon by a sub-committee for presentation to the full Board, but had not yet been resolved; and another approximately sixty cases are currently under active investigation.

Personal Reflections

I wish to offer some personal reflections on one year of experience as a novice, viewpoints which do not necessarily represent official positions of our Board.

(1) I am deeply impressed by the balanced competence of the board members, their dedication, commitment, and integrity. There has not been any indication of a "let's get the Doc" attitude: there is an equally firm resistance to "sweeping any unpleasantness under the rug." I believe also that our staff members have been efficient, courteous, and helpful to the public and the medical community as we consider ourselves servants of the public.

(2) We consider our prime responsibility to be the protection of the public from physicians categorized as practicing at a level of unprofessional conduct. We take equally seriously our obligations for fair and equitable and confidential treatment of each physician with full provision of due process.

(3) Our most difficult task has been to differentiate consistently and in a manner defensible to most reasonable physicians or community members between a human mistake that any or all physicians as human beings may make versus an act of unprofessional conduct, particularly the first such event brought to our attention involving a physician of good reputation. This difficult,

even impossible task is compounded by a deep mistrust by many in the possibility of full confidentiality now or in the future coupled with the major criticism (or worse) directed at our Board — namely the terrible damage to a physician as well as to his/her family, his/her patients, and other referring physicians by the public disclosure mandated by law. We are deeply sensitive to, we have agonized at great length over, this issue. Although our highest priority is to identify any pattern of repetitive individual unprofessional conduct and although we believe that it is difficult in certain instances to define any real benefits to members of the public of public disclosure by the media, we believe we must obey our mandate, independent of individual *a priori* bias or discrimination in favor of the “good doctor” or against the putative “bad doctor.”

(4) The public and its spokespersons need a great deal of education to understand better that any unfortunate outcome of a medical or surgical encounter does not automatically represent substandard care, justifying a complaint or malpractice claim. We are not interested in any numbers game. The majority of insurance company settlements reviewed by the Board did not, in our judgment, represent substandard care by physicians. Rather they appear to have been made because of questionable (or probable) liability, concern over the unpredictability of a trial by jury, or primarily socio-economic considerations (such as the physician's level of insurance coverage, the problem of large additional interest charges over time, or both).

(5) We believe also that we may serve a valid role in educating physicians by reporting on certain generic issues involved in complaints to, and decisions and sanctions by, the Board. The genesis of a large number of complaints, other than unsatisfactory results, appears to be a perceived lack of, or inappropriate communication between the physician or his/her office staff and aides and the patient. The Board does not generally engage in fee disputes, considering those a matter between patient and doctor, unless, as mandated by item 16 of the list of unprofessional conduct, there is evidence of “gross and willfull overcharging for professional services.”

Conclusion

I believe I do speak for the Board when I state, “We welcome any criticisms” (particularly if accompanied by suggestions for improvement) in the ways our Board is trying to carry out its mandate.



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Protecting Physicians' Rights In Disciplinary Proceedings

Ensuring that the Physician Receives a Fair Hearing Before Disciplinary Action is Taken is the Function of Due Process

John H. Reid, III

Doctor King* has asked me to discuss the legal concept of due process as it applies to physicians participating in and subject to the various disciplinary proceedings which are currently in use to control the quality and cost of health care. Discipline of physicians is the responsibility of Health Care Review, Inc (HCR), the state Board of Licensure and Discipline, Blue Cross and Blue Shield of Rhode Island (Blue Cross) as the agent of the federal Health Care Financing Administration (HCFA) in the Medicare context, and various hospital peer review committees. Each of these organizations has investigatory powers. The exercise of these powers can result in a formal hearing at which a determination is made whether the physician has violated a rule, regulation or law. An adverse determination against the physician at the hearing can result in a fairly serious sanction, such as suspension from Medicare, loss of staff privileges or loss of license.

John H. Reid, III, is a partner with the firm of Edwards and Angell in Providence, Rhode Island and Legal Counsel for the Rhode Island Medical Society.

The following paper was read at the 44th Charles V. Chapin Oration at Rhode Island Hospital, October 13, 1988.

* Boyd P. King, MD, president of the Rhode Island Medical Society.

The function of due process is to ensure that the physician receives a fair hearing before disciplinary action is taken. Due process includes the following rights of the physician who is the subject of the investigation:

1. Adequate notice of the charges made and a reasonable opportunity to respond to those charges;
2. An opportunity to confront and cross-examine the person making the accusation and to examine and refute evidence;
3. Reasonable opportunity to present a defense; and
4. A hearing before an impartial decision-maker.

In my experience as a lawyer who represents individual physicians, due process is most frequently threatened during the investigation of the physician's practices by the enforcement organization. For instance, as the result of a Blue Cross/Medicare investigation of a urologist, Blue Cross proposed to recoup a substantial amount of fees for what were deemed to be unnecessary x-ray studies. The recoupment letter did not identify who had made the determination that the x-ray studies had been unnecessary or the specifics as to why the determination was made. The review of the x-ray records had been done by an internist, who was not familiar with normal urological procedures. This information became known only after the doctor challenged the Blue Cross determination and submitted a substantial

amount of evidence to support his position. In this case, Blue Cross ultimately allowed the charges. I wonder how many doctors receive recoupment notices and pay the amount demanded by Blue Cross without fully understanding why their charges have been disallowed.

Of course, part of the problem is lack of knowledge on the part of the physician of what constitutes proper charges. HCFA refuses to publish the screens it uses to determine who should be investigated. Misconceptions exist concerning what are proper billing codes. It is difficult to find clerical personnel to supervise billing practices who are thoroughly familiar with the reimbursement regulations.

Fortunately, most Medicare reviews conducted by Blue Cross result only in recoupment of fees paid and are settled with Blue Cross. However, if the physician does not agree with the final Blue Cross determination and if the amount in issue exceeds \$500.00, the physician now has the right to appeal the Blue Cross decision to an Administrative Law Judge. If the amount involved exceeds \$1,000.00, an adverse decision by the Administrative Law Judge can be appealed to federal district court. These new procedures apply to claims filed after January 1, 1987.

In the case of the Board of Licensure and Discipline, once an investigating committee has been assigned to a particular case, the physician under investigation is invited to meet with the committee at an informal conference to discuss the matter. Although the physician is advised of the complaint that has resulted in the investigation, he goes to the conference without knowing the entire record on which the decision to investigate was made. The members of the investigating committee may have knowledge, either first-hand or second-hand, of events which color their attitude toward the physician. To prepare an adequate defense, the physician would need to produce evidence or testimony which would rebut the negative inferences from those other events. The Board permits the physician to appear with his lawyer because of the need to protect his rights. It is advisable to include the lawyer at this point to avoid making damaging statements at the conference and to develop a better understanding of the case.

It may be said that as long as the physician is advised of all of the factors on which the disciplinary action is based prior to a formal hearing, he is receiving due process. Although that may be true, it is not particularly comforting to the physician during the investigatory phase. He is

apt to feel threatened by the investigation itself and should be given a reasonable opportunity to clear himself before the formal hearing stage is reached. After all, the investigating committee can recommend that no action be taken against the physician.

The American Medical Association (AMA) recently challenged the constitutionality of the Professional Review Organization (PRO) sanction process in court and was able to reach a settlement with the government that goes a long way toward ensuring that physicians receive due process in the PRO system. Under the settlement:

1. Physicians are to receive a detailed initial notice explaining the alleged violation, the facts relied on by the PRO, the importance of the meeting with the PRO and the potential consequences of a sanction;
2. Physicians involved in the investigation are excluded from voting on the final sanction recommendation;
3. Physicians under review have the right to be represented by counsel;
4. Physicians are entitled to present witnesses and evidence and to ask clarifying questions of PRO witnesses.

Generally speaking, these four items present a blueprint for preserving due process in any disciplinary proceedings.

Another recent concern about due process has been the question of the impartiality of the decision-maker. Both the PRO procedures described above and the statute governing the Board of Licensure and Discipline prohibit investigators from participating in sanction decisions. This helps preserve impartiality.

In the case of *Patrick v Burget*, 108 S Ct 1658 (1988), the United States Supreme Court decided that physicians who participate in the peer-review process may be liable for breach of the federal antitrust laws. Because of this decision, much attention has been focused on the potential liability of physicians who participate in peer-review activities. In fact, so much attention has been focused on that aspect of the case that the Congress, as part of the Health Care Quality Improvement Act of 1986, provided a specific exemption for peer review activities in the following circumstances:

1. The disciplinary action taken must be in the reasonable belief that it promoted quality health care;

2. There must have been reasonable efforts to obtain the relevant facts of the situation;

3. There must be adequate notice and hearing procedures afforded the physician being sanctioned; and

4. There must be a reasonable belief that the professional review action was warranted by the facts.

The aspect of the *Patrick* case which I want to highlight now is the fact that the decision to recommend termination of Doctor Patrick's privileges was made by a committee composed in part of the physicians with whom he was in direct economic competition. When Doctor Patrick first began to practice, he had been an employee of these physicians and had subsequently left them to start his own practice. Even if there were valid grounds for terminating his staff privileges, the fact that his competitors were part of the committee tainted the decision. As a general rule, when a court sees a situation in which an individual has been deprived of a valuable right by a process that appears to be tainted, the court will find a way to protect the rights of the individual who has received unfair treatment.

Notwithstanding the Health Care Quality Improvement Act, if the peer review process is used to further the interest of private individuals rather than the public, participants in the process may have some liability. On the other hand, where the disciplinary process is used to promote better health care, physicians participating in the process should have no liability.

Rhode Island has its own statute providing immunity to physicians who participate in peer-review activities (Section 23-17-25 of the *General Laws of Rhode Island*). However, the Rhode Island and the federal statutes do not prohibit suit — they only provide protection against liability. Therefore, it is imperative that the peer review process be kept impartial and fair in order to reduce the risk of suit and limit the participating physicians' liability.

Conclusion

We should recognize that the political forces which bear on the health-care industry will result in more disciplinary proceedings. A representative of Blue Cross recently told the Executive Committee of the Medical Society that HCFA reviews the Medicare disciplinary proceedings annually and has already notified Blue Cross that the sanctions procedures will be completely revised to result in tougher reviews and greater

incidence of the imposition of penalties and may even include a bonus system. I assume similar instructions will be given to HCR. In this environment physicians need to be aware of their rights to a fair hearing and must assert those rights vigorously.

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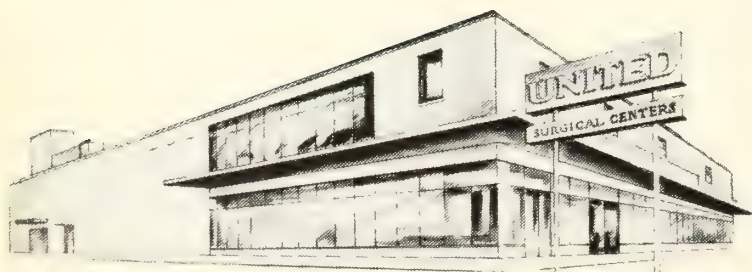
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SPECIAL REPORT

Screening Criteria for Prior Authorization for Ten Surgical Procedures

Drafted by the Rhode Island Professional Review Organization (PRO) for the Preadmission-Preprocedure Review Program

Health Care Review, Inc., the PRO for Rhode Island, has been directed by the Health Care Financing Administration (HCFA) to implement a Preadmission-Preprocedure Program for ten specified surgical procedures. The review was mandated "to determine the medical necessity of the procedure, the appropriateness of the setting, and the quality of service provided." The ten surgical procedures are:

- 1 Total Joint Replacement
 - a Total Knee
 - b Total Hip
- 2 Lumbar Laminectomies
- 3 Repair of Inguinal Hernia
- 4 Cholecystectomy
- 5 Transurethral Prostatectomy (TURP)
- 6 Carotid Endarterectomy
- 7 Coronary Artery Bypass Graft (CABG) and
- 8 Angioplasty, Percutaneous Transluminal (PTCA)
- 9 Cataract Removal
 - Assistant at Cataract and Intraocular Lens (IOL) Surgery
- 10 Hysterectomy
 - a Abdominal
 - b Vaginal

During November 1988 Health Care Review, Inc. informed Rhode Island's surgeons of the proposed implementation of the screening process and provided sample preprocedure request forms. In response to an inquiry from the Rhode Island Medical Society, the screening criteria for the ten procedures were provided. The criteria are subject to revision in response to feedback

from the various specialty societies in the state, and the package must be approved by HCFA in Washington, which may mandate changes in the criteria and the program. The proposed criteria for the various procedures are here provided to our members for informational purposes.

Criteria For the Ten Surgical Procedures

TOTAL KNEE REPLACEMENT

- A Knee Pain [refractory pain at least six (6) months.]
- B Patient requires help with activities of daily living [needs two (2) of the following]:
 - 1 Dressing;
 - 2 Difficulty on stair ambulation;
 - 3 Instability on uneven surfaces;
 - 4 Use of cane, walker, or crutches for ambulation.
- C Clinical Examinations [three (3) or more]
 - 1 Swelling (synovial thickening and/or effusion)
 - 2 Painful and limited range of motions
 - 3 Crepitus
 - 4 Standing deformity
- D X-ray [one (1) or more indication(s)]
 - 1 Showing degenerative changes indicating moderate to severe disease (joint space narrowing, spurring, and incongruity).
 - 2 Standing deformity (valgus varus).
- E History
 - 1 Chronic knee pain of at least six (6) months duration.

- 2 Failure of conservative treatment for at least six (6) months to control symptoms (cane, medication, brace, injection, physical therapy).

NOTE TO NURSE REVIEWER: The nurse reviewer can approve a case if Section A is met as well as one (1) from sections B, C, D, or E are met, otherwise the case must be referred to a physician reviewer.

TOTAL HIP REPLACEMENT

- A Hip pain [refractory pain at least six (6) months duration].
- B Requiring help with activities of daily living [one (1) or more indications]:
 - 1 Dressing;
 - 2 Difficulty on stair ambulation;
 - 3 Difficulty arising from low sitting position;
 - 4 Requiring use of cane, walker, or crutches for ambulation.
- C Clinical examination including both:
 - 1 Painful or significant diminished range of hip motion in any plane (greater than 10 degrees loss);
 - 2 Awkward, weak or painful gait.
- D X-ray (one or more indications):
 - 1 Radiologic evidence of joint narrowing or incongruity, spurring, or avascular necrosis;
 - 2 Radiologic evidence of prior hip joint fracture resulting in progressive secondary osteoarthritis;
 - 3 Radiologic evidence of comminuted fracture of the femur, head, and/or neck.
- E Patient's principal diagnosis must include one (1) of the following, or else refer to a physician reviewer:
 - 1 Osteoarthritis primary or secondary;
 - 2 Rheumatoid arthritis;
 - 3 Avascular necrosis;
 - 4 Gouty arthritis

NOTE TO NURSE REVIEWER: The nurse reviewer can approve a case if Section A and at least one indication from Sections B, C, and D are met, otherwise the case must be referred to a physician reviewer.

LUMBAR LAMINECTOMIES

- A Presence of malignancy with acute neurologic deficit.

- B Presence of acute trauma with acute neurologic deficit.
- C Positive myelogram, CT scan or MRI and one of the following:

- 1 Neurologic deficit evidenced by one of the following:
 - a Leg pain or claudication confirmed by history;
 - b Weakness of leg confirmed by physical exam;
 - c Numbness of leg confirmed by physical exam.
- 2 Foot drop
- 3 Bladder or bowel dysfunction
- 4 Sexual dysfunction
- 5 Failure of medical treatment (i.e., physical therapy, medications, traction, braces) for a sixty (60) day time period

NOTE TO NURSE REVIEWER: Nurse reviewer may approve if A, B, or C is met.

REPAIR OF INGUINAL HERNIA

- A Demonstrable inguinal hernia without symptoms in ASA I or II patients.
- B Symptomatic hernia or ineffectual truss in ASA III or IV patient.
- C Information to request or review:
 - 1 physical exam shows evidence of hernia;
 - 2 pain and/or discomfort and failure of the truss to maintain reduction of hernia.

NOTE TO NURSE REVIEWER: You may approve the case on an outpatient basis if A is checked and procedure is to be performed with local anesthesia; on an inpatient basis if B is checked and the procedure is performed with general anesthesia.

CHOLECYSTECTOMY

- A Preoperative indications:
 - 1 Acute cholecystitis with two (2) or more of the following:
 - a Pain;
 - b Elevated white blood count;
 - c Elevated temperature of 100 degrees F (38 degrees C) or greater;
 - d Nausea and vomiting;
 - e Abnormal LFTs
 - f Positive stones.
 - 2 Cholelithiasis with symptoms of recurrent abdominal pain and/or elevated tempera-

ture of 100 degrees F (38 degrees C) or greater.

- 3 Choledocholithiasis
- 4 A tumor of the gallbladder
- 5 Chronic Cholelithiasis with Diabetes Mellitus

B Information to request:

- 1 Request radiologic (imaging-ultrasound) evidence with confirmation of diagnosis.
- 2 Request evidence for stones in the common bile duct.

NOTE TO NURSE REVIEWER: You may approve if any criteria is met, numbers 1 through 5.

TRANSURETHRAL PROSTATECTOMY (TURP)

A Symptoms of urinary obstruction: (three or more indications)

- 1 Progressively weak stream
- 2 Frequency
- 3 Hesitancy
- 4 Urgency
- 5 Nocturia
- 6 Incontinence
- 7 Hematuria
- 8 Post void residual, greater than 200 cc.

B Radiological or physical evidence of prostatic obstruction, as evidenced by (one or more indications)

- 1 Diverticuli of bladder shown on IVP or ultrasound;
- 2 Bladder stones developing;
- 3 Bleeding from prostate;
- 4 Recurrent urinary tract infection;
- 5 Renal failure related to obstruction;
- 6 Hydronephrosis and/or hydroureter on IVP; abnormal urinary track ultrasound residual volume greater than 100 cc.
- 7 Flow rate less than 10 ml/sec.

NOTE TO NURSE REVIEWER: You may approve the case if three (3) or more indications are checked for A and one (1) or more for B.

CAROTID ENDARTERECTOMY

A Nurse reviewer is to refer all requests for endarterectomy to a physician reviewer.

B Specific questions for request for information:

- 1 List symptoms;
- 2 List results of tests with documentation, for example bilateral A-grams, CT scans;

3 List other medical problems which the patient has;

4 List indications for the procedure.

CORONARY ARTERY BYPASS GRAFT (CABG) AND ANGIOPLASTY, PERCUTANEOUS TRANSLUMINAL (PTCA)

A One of the following:

- 1 Angiography demonstrates left main coronary stenosis greater than 50 per cent;
- 2 Angiography demonstrates stenosis greater than 70 per cent of one or more major coronary artery(s) and patient has symptoms refractory to medical therapy.
 - a If the patient is on three (3) medications and still symptomatic, this is considered refractory to medical therapy.
- 3 Significant three (3) vessel disease with poor left ventricular function;
- 4 Emergency CABG after complications of PTCA;
- 5 Failure of thrombolytic therapy;
- 6 Restenosis after PTCA.

B Questions to retrieve data:

- 1 What is the indication for performing PTCA/CABG?
- 2 List signs, symptoms, and arrhythmias.
- 3 List cardiac catheterization results.
- 4 List medications which the patient is on.
- 5 Past medical history.

NOTE TO NURSE REVIEWER: You may approve if any criteria are met, numbers 1 through 6.

INDICATION TO PERFORM CATARACT REMOVAL

1 Presence of cataract requiring lens extraction, eye exam reveals:

A Phacocanaphylaxis or phacolytic glaucoma: Cells and flair, swollen or mature lens, elevated pressure in affected eye (normal pressure between 22 and 25 mm Hg).

B Angle closure glaucoma secondary to cataract:

Angle closure present by gonioscopy or observation and cataract present. Acute increase in pressure documented.

C Subluxation or dislocation of lens causing glaucoma:

Evidence of subluxation/dislocation on eye exam.

2 Presence of cataract has resulted in decreased visual acuity limiting daily activities, employment, reading, recreation.

- 3 Cataract prevents diagnosis or treatment of other diseases listed below (at least one): diabetic retinopathy, hypertension retinopathy, glaucoma, retinal detachment or high risk of retinal detachment, optic neuropathy, papilledema, vitreous hemorrhage, or tumor.
- 4 If optic nerve is abnormal, refer to physician reviewer.
- 5 Expected Outcome:
 - A If no functional improvement expected, refer to physician reviewer.
 - B If expected visual acuity improvement is not at least two lines better on Snellen chart, refer to physician reviewer: 20/10, 20/13, 20/15, 20/20, 20/25, 20/30, 20/40, 20/50, 20/70, 20/100, 20/200.

NOTE TO NURSE REVIEWER: Nurse reviewer may approve if #1 and #2, #2 and #3 or #2 and #5 are met, and the optic nerve and retina are normal.

ASSISTANT AT CATARACT SURGERY

Nurse coordinators may approve the use of an assistant surgeon on all cases where at least one criterion is met. Where no criteria are met the case must be referred:

- I SIGHT IN THE NON-OPERATIVE EYE
 - A Noncorrectable visual acuity of 20/200 or less, or
 - B Noncorrectable fields limited to 10 per cent fixation.
- II MULTIPLE OPHTHALMIC PROCEDURES

Cataract extraction *plus* any one of the following:

 - A Anterior segment repair;
 - B Vitrectomy;
 - C Retina surgery;
 - D Glaucoma surgery, Trabeculectomy.
- III PREVIOUS COMPLICATION IN NON-OPERATIVE EYE ENCOUNTERED DURING SURGERY

Previous complication during surgery in the non-operative eye with expectation of recurrence and placing patient at high risk. Any one of the following:

 - A Vitreous loss;
 - B Hemorrhage;
 - C Retinal detachment.
- IV BLEEDING RISKS

Bleeding disorders making the patient high risk. Any one of the following:

 - A Hemophilia;
 - B von Willebrand's.

V POSITIONAL PROBLEMS

Any chronic condition disabling the patient to the extent that surgery cannot be performed in the supine position.

VI UNCOOPERATIVE PATIENT

Refer all cases.

VII OTHER

Juvenile cataract age less than or equal to 35 years.

HYSTERECTOMY

- A Hysterectomy, abdominal, with or without bilateral salpingo-oophorectomy
 - 1 Uterine leiomyoma with either
 - a abnormal uterine bleeding* [continued severe bleeding after several menstrual periods, and two (2) nondiagnostic D&Cs]* or
 - b progressive enlargement of uterus after menopause, and benign endometrial sample.
 - 2 ALL OF THE FOLLOWING
 - a Recurrent abnormal uterine bleeding* (excluding patients on birth control pills or patients with IUDs).
 - b Benign endometrial sample.
 - 3 BOTH
 - a Clinical diagnosis of endometriosis or suspicious for endometriosis (dysmenorrhea, infertility), and
 - b Failure of nonsurgical management (i.e., birth control pills, danazol).
 - 4 Adenomatous hyperplasia demonstrated by findings of dilatation and curettage (D&C).
 - 5 Adenocarcinoma of the endometrium demonstrated by dilatation and curettage (D&C).
 - 6 Pelvic mass suspicious for ovarian malignancy.
 - 7 Cervical intraepithelial neoplasia.
- B Hysterectomy, vaginal
 - 1 Premalignant lesion of endometrium.
 - 2 Continued severe bleeding after several menstrual periods and two (2) nondiagnostic D&Cs.
 - 3 Hysterectomy with vaginal repair of cystocele, rectocele or enterocele.
 - 4 Uterine prolapse, second or third degree.
 - 5 Adenomyosis uteri.
 - 6 Cervical intraepithelial neoplasia.

*The parentheses above denote recurrent abnormal uterine bleeding. Postmenopausal bleeding is the same as bleeding for one (1) year after menopause and after one (1) D&C.

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**Radiologic Case of
the Month**

(answer on page 77)



At the time of a routine physical examination, an asymptomatic 52-year-old woman is found to have an alkaline phosphatase level six times normal. Past medical history reveals a terminal ileal resection for Crohn's disease 5 years earlier with no recurrent symptoms. Isoenzyme studies revealed the alkaline phosphatase to be of liver origin. There is no history of hepatitis or epidemiologic clues to possible liver disease. CT scan of the liver reveals dilated bile ducts. A cholangiogram is then performed via ERCP.

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Manuscripts: Manuscripts will be accepted for consideration with the understanding that they are original contributions, have never been published or submitted elsewhere, and are submitted only to the *Rhode Island Medical Journal*.

Specifications: Manuscripts must be original typed copy (not all capitals) on 8½x11 inch firm typewriter paper, double-spaced (including the text, case reports, legends, tables, and references) with 1½ inch margins. Carbon copies will not be accepted. Subheadings must be inserted at reasonable intervals to break the typographic monotony of the text. Pages must be numbered consecutively. Italics and boldface print are never used except as subheadings.

Abbreviations: The *Journal* attempts to avoid the use of jargon and abbreviations. All abbreviations, especially of laboratory and diagnostic procedures, must be identified in the text.

Title page: All manuscripts must include a title page which details the following information: (1) a brief title; (2) the name of the author or authors with the highest academic degree (ie, MD, PhD); (3) a concise biographical description for each author which includes specialty, practice location, academic appointments, and primary hospital affiliation; (4) mailing address of principal author; and (5) office telephone number of principal author.

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Special arrangements must be made with the editors for excessive illustrations. Color plates are not acceptable.

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It is rarely desirable to include a complete review of the literature in the references. An alphabetized bibliography is to be used only when the listing is of books suggested for supplementary reading.

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Recent Abstracts of Interest

Public Health

Edited by Edward R. Feller, MD

Clinical Ethics Consultations May Be a Useful Resource

A recent study evaluated clinical ethics consultations at a University Medical Center over an 18-month period. The purpose was to assess consultation impact via retrospective chart review and questionnaires for physicians requesting consultations. The paper outlines the organization of an ethics consultation service. A consultation request is followed by chart review and interviews with the patient, family, physicians, and other care givers to identify ethical issues present (defined as any conflict of values affecting patient care). A member of the Ethics Committee then meets with the requesting physician to suggest ways to resolve the issues. All recommendations are non-binding. The most prevalent issue in this study was whether or not to use a specific therapy, most commonly cardiopulmonary resuscitation or mechanical ventilation. Other common issues were the need for a proposed surgical procedure, the appropriateness of ICU care, as well as issues involving the competence of patients to express preferences for treatment and appointment of proxies for decision making for both children or adults. Results of chart review or questionnaires suggested that ethics consultations had considerable impact on objective decision making. Discussion of ethical considerations in patient care also appeared

to have other less easily measurable subjective benefits to care givers.

Perkins HS, Saathoff BS: Impact of medical ethics consultations on physicians; an exploratory study. *Am J Med* 85:761-765, Dec. 1988.

Difficulty in Assessing the Economic Impact of AIDS

Limitations in data exist in presently available estimates of personal and national health-care costs of AIDS. Empirical studies of personal health-care costs of AIDS have generally been retrospective based on patients' medical and financial records and involving limited numbers of cases, especially limited to in-patient services. The author describes differences in results based on conflicting underlying assumptions regarding the projected number of cases with AIDS, the lifelong medical cost per case, the lack of outpatient data, as well as uncertainty of the effect of a change in the future case mixed with emergence of a greater number of IV drug abusers with HIV infection.

The author attempts to assess the impact of AIDS on hospitals using a 1991 estimate of 5.9 million hospital days for inpatient care of AIDS patients. A figure equivalent to 2.6 per cent of all hospital days. This figure is almost four times

the number of days used by patients with carcinoma of the colon or carcinoma of the breast. The author makes recommendations for future studies including the need for prospective studies following patients for extensive periods, development of more accurate data on insurance coverage of AIDS patients, and improved data of prevalence of HIV infection.

Scitovsky AA: The Economic impact of AIDS in the United States. *Health Affairs* 7:32-45, 1988.

Nutritional Modulation Effects on Successful Aging

This ULA clinical conference discusses the interaction of nutrition and aging. Topics include both age-related alteration in nutritional state and impact of nutrition on health and life expectancy. There is a detailed assessment of causes of anorexia of aging including social (isolation, financial), normal physiologic changes of aging as well as abnormal changes including decreased ability to chew, the effect of intercurrent medical illness, depression, and cognitive dysfunction as well as decreased feeding drive and increased satiety. A section is devoted to analysis of caloric intake, protein, carbohydrate, and fat metabolism. Vitamins may be abused by elderly individuals. Medication may increase or decrease appetite, interfere with nutrient absorption or utilization, and increase financial constraints limiting adequate dietary intake. There is a pertinent discussion of trace metal deficiency and its consequences. This is a comprehensive clinically relevant review of nutrition and aging.

Morley JE, Mooradian AD, Silver AJ, Heber D, Alfin-Slater RB: Nutrition in the elderly. *Annals Int Med* 109:890-904, Dec. 1988.

drinking. Four and 6/10 million adolescents in the United States experience problems with alcohol each year. One of two teenage deaths in auto accidents involve alcohol use. In one-half of all teenage pregnancies, one or both parents had been drinking at the time of conception. Alcohol is involved in one-third of all child molestation cases.

The average monthly health-care bill for families having an alcoholic member is twice that of families not containing an alcoholic. Between six and seven million employed American workers are alcoholics. In this government report it is estimated that alcoholics cost our economy approximately 117 billion dollars per year, most from reduced worker productivity and lost employment. This report outlines the general approach of the Department of Health and Human Services in prevention and reduction of alcoholism. Included are suggestions to expand advertising utilizing prominent persons who are recovered alcoholics and an opinion that equal time on television is needed to counterbalance "slick, pervasive and persuasive" TV commercials. The authors also describe federal programs in which 2.2 million government employees have access to alcohol treatment and also briefly discuss programs of the National Institute of Alcohol Abuse and Alcoholism. The paper is without annotation or references, so that the source of the figures given is unclear.

Burke TR: The Economic impact of alcohol abuse and alcoholism. *Public Health Reports* 103:564-568, Nov.-Dec., 1988.

Alcohol is the Foremost Drug Abused in the United States Today

A recent paper presents an overview of official national policy assessment of alcoholism and its consequences by an economist in the Department of Health and Human Services. The paper is part of a symposium in an issue devoted to alcoholism. This report outlines the magnitude of underage

PERIPATETICS

The Memorial Hospital of Rhode Island has recently appointed **Dr David L. Horn** to the internal medicine staff. **Dr Horn** will also serve as medical director of the NewHealth Center in Providence.

• • •

Dr Young Shin Chee, a specialist in anesthesiology, was recently appointed to the medical staff of South County Hospital.

• • •

The American College of Surgeons recently elected **Dr A. Gerson Greenburg** to a second term of membership and Vice Chairman on the Pre- and Postoperative Care Committee.

• • •

Five new physicians have been appointed to the medical staff of Westerly Hospital: **Dr Dominick Cannone**, nephrologist; **Dr John Andrew Hallberg**, orthopedic surgeon; **Dr Allen V. Hurt**, plastic and hand surgeon; **Dr John A. Pagnozzi**, general surgeon; and **Dr Anne E. Wood**, obstetrician/gynecologist.

• • •

Recently in Caracas, Venezuela as Visiting Professor to the University Hospital of Venezuela giving rounds in Endocrinology, **Dr Ivor Jackson** was the special guest lecturer at a symposium on Hypothalamic-Pituitary Disease sponsored by the University of Caracas, Department of Endocrinology and Metabolism.

• • •

Brown University recently honored **Dr Stanley M. Aronson**, specialist in pathology and neurosciences, and **Dr Sanford W. Udis**, clinical associate professor at Brown specializing in diagnostic imaging, at the school's 12th Annual Medical Recognition Dinner for their "distinguished service to medical education in Rhode Island."

Are You Concerned About the Competence of a Certain Physician?

If so, the Peer Review Committee on Physician Competency can offer discreet and effective help. A standing committee of the Rhode Island Medical Society since 1985, the Peer Review Committee works in a completely confidential, supportive way to help assure that physicians consistently meet minimum acceptable standards of medical practice. The primary work of the Committee is to help physicians improve the quality of their care through education.

If you know a physician who can benefit from peer education in a particular area of medical practice, please write Dr. William Colaiace, Chairman, Peer Review Committee on Physician Competency, Rhode Island Medical Society, 106 Francis Street, Providence, RI 02903. For more information, call the Society at (401)331-3207. All referrals are held in strict confidence.

*Answer to Radiologic Case of the Month
(from page 71)*

Diagnosis:

Sclerosing cholangitis represents an obliterative process of large bile ducts in which there is irregular luminal narrowing producing a diffuse beaded appearance on cholangiography. Typically, the entire intrahepatic biliary tree and frequently the extrahepatic biliary tree are involved. However, the process can be limited to only part of the biliary ducts. Up to one-third of cases have a history of ulcerative colitis and less commonly Crohn's disease. Recently, patients with AIDS have been reported with a sclerosing cholangitis-like picture sometimes associated with cytomegalovirus (CMV) or cryptosporidial infection of the bile ducts. Some evidence suggests that sclerosing cholangitis is an immunologic process. Localized sclerosing cholangitis may be impossible to differentiate from cholangiocarcinoma. Although some patients are asymptomatic when diagnosed, most have jaundice due to biliary obstruction and eventual development of secondary biliary cirrhosis. Chills and fever indicative of biliary infection are common.

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Contraindications: VASOTEC[®] (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Warnings: *Angioedema:* Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Heart failure patients given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in heart failure patients), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, *Drug Interactions* and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: *General:* **Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: Elevated serum potassium (> 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See *Drug Interactions*.)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes; lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: *Patients on Diuretic Therapy:* Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methylglucoside, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium: A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. Although a causal relationship has not been established, it is recommended that caution be exercised when lithium is used concomitantly with VASOTEC and serum lithium levels should be monitored frequently.

Pregnancy—Category C. There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was used to cross the placenta following administration of labeled enalapril to pregnant hamsters.

There are no adequate and well-controlled studies in pregnant women. VASOTEC[®] (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Milk in lactating rats contains radioactivity following administration of ¹⁴C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 298 patients.

Hypertension: The most frequent clinical adverse experiences in controlled trials were headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

Heart Failure: The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

Cardiovascular: Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, *Hypotension*), cardiac arrest, pulmonary embolism and infarction, rhythm disturbances, atrial fibrillation, palpitation.

Digestive: Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis.

Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), prostate hypertrophy.

Respiratory: Bronchospasm, rhinorrhea, asthma, upper respiratory infection.

Skin: Herpes zoster, pruritus, alopecia, flushing, photosensitivity.

Other: Muscle cramps, hyperhidrosis, impotence, blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include fever, myalgia, and arthralgia; an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Clinical Laboratory Test Findings

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who are also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol %, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

Dosage and Administration: *Hypertension:* In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions*.)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium. (See PRECAUTIONS.)

Dosage Adjustment in Hypertensive Patients with Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure: VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, *Drug Interactions*.) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics and Clinical Effects*.) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

Dosage Adjustment in Heart Failure Patients with Renal Impairment or Hyponatremia: In heart failure patients with hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine > 1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, *Heart Failure*, WARNINGS, and PRECAUTIONS, *Drug Interactions*.) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

For more detailed information, consult your MSD representative or see Prescribing Information, Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19386.

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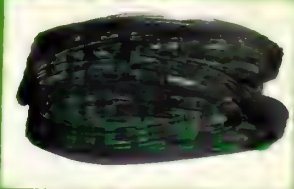
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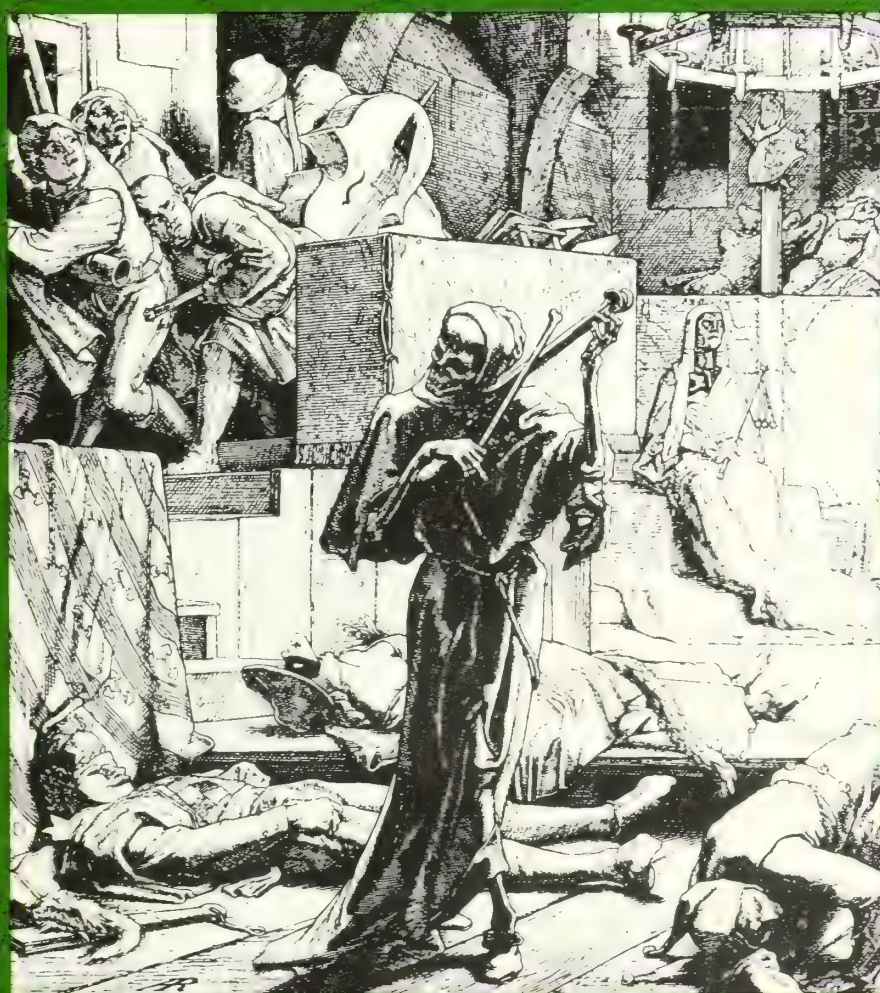
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Volume 72, Number 3



*Society's Influence
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(See page 93)

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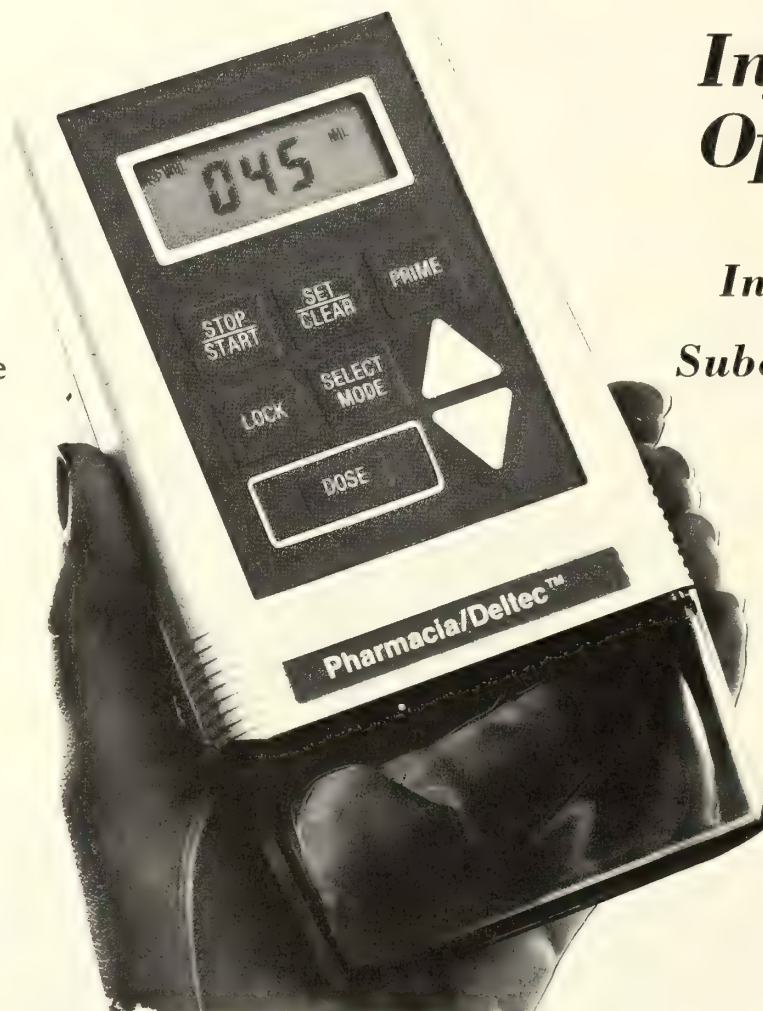


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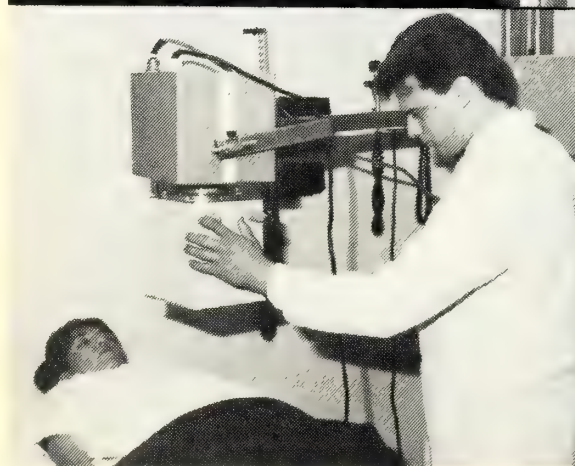
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EDITORIAL

The Golden Age of Pharmacology

While we tend to look upon the second half of the Twentieth Century as the age of molecular biology, biotechnology, and genetics with seminal discoveries in the structure of DNA and gene splicing, important advances have been made in pharmacology and chemical therapeutics. Recognition of this fact has led the Harvard Medical School recently to combine the departments of Biochemistry and Pharmacology into a single department of Biological Chemistry and Pharmacology. The Nobel Assembly awarded the 1988 prize in Physiology or Medicine for pioneering developments in pharmacology. The three recipients of the prize are George Hitchings, PhD and Gertrude Elion, DSc, both of the Burroughs Wellcome Co of Research Triangle Park, North Carolina, and Sir James W. Black of King's College Hospital Medical School of the University of London.

The announcement of the Nobel Assembly stated, "The discoveries awarded in this year's Nobel Prize in physiology or medicine concern important principles in drug treatment, principles that have resulted in the development of a series of new drugs."

In the 1950s and 1960s Elion and Hitchings developed drugs useful in the treatment of gout, leukemia, and malaria. These include 6-mercaptopurine and thioguanine. Later they developed azathioprine, beneficial in autoimmune disease and important in immunosuppression in the early organ transplantations. Allopurinol proved valuable in the treatment of gout. More recently they have introduced acyclovir in the treatment of genital herpes and zidovudine which has shown promise in suppressing the symptoms of AIDS.

Black was the discoverer of drugs which could block B-adrenergic receptors, thus inhibiting the action of adrenaline. He developed propranolol hydrochloride, the first of this class of agents. He

later explored the possibility of developing molecules that could block the histamine receptors responsible for the secretion of gastric juice. This led eventually to the development of cimetidine, the first drug that directly controls peptic ulcer by inhibiting gastric juice secretion.

This galaxy of pharmacological advances typifies the new Golden Age of Pharmacology.

Seebert J. Goldowsky, M.D.

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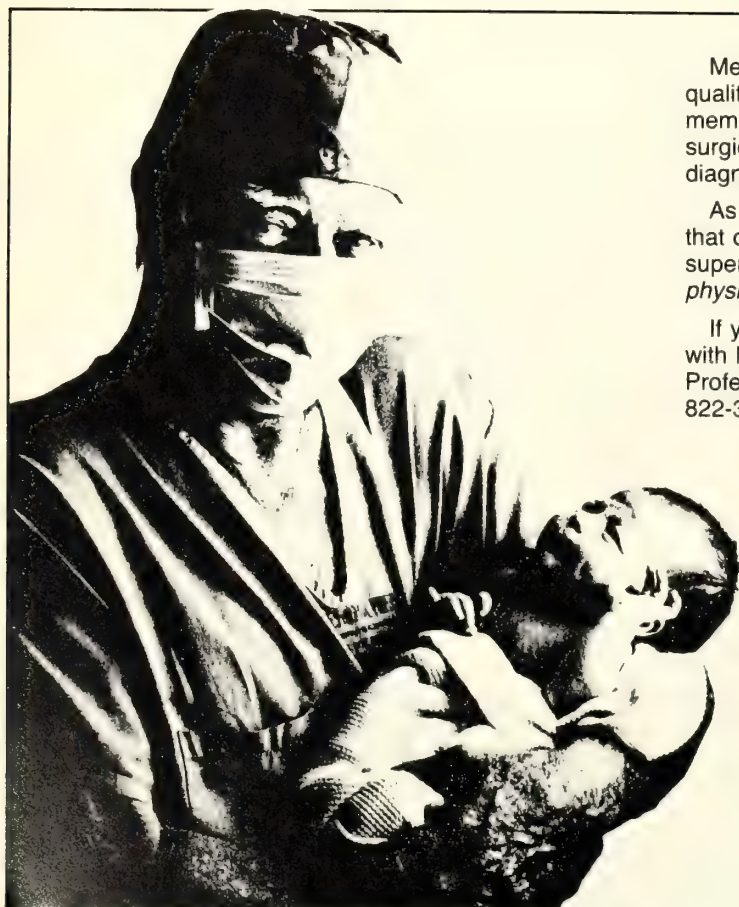
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ADDRESS
ON THE RELATIONS OF THE YOUNG PHYSICIAN TO THE PROFESSION
AND THE PUBLIC.

BY
H.G. STICKNEY, M.D.,
OF PROVIDENCE.

READ BEFORE THE RHODE ISLAND
MEDICAL SOCIETY, AT THE SEMI-ANNUAL
MEETING, DEC. 19TH, 1860

Mr. President and Gentlemen:

I fear it will be thought unseemly for a tyro, if in the presence of these war-worn veterans, he should attempt to sketch the dangers of the field where they have spent their lives in active service, and reaped noble laurels as the reward of successful toil. Yet, craving your kind indulgence for venturing on such a theme, I will endeavor briefly to set forth a few of the trials and temptations, as well as pleasures, to be expected by the young physician: also, to say a few words upon medical epidemics. His pupilage, as that term is generally understood, is passed, its pleasures enjoyed, its difficulties surmounted, his energies have been faithfully employed in the acquirement of his profession. He has received the approbation of his instructors, and the honors of his College; he has true ideas of the obligations which he owes to society and to his profession, and some decided aspirations after a true success and honestly acquired fame.

Thus prepared, the question, if it has not already been proposed and definitely answered, meets him with an almost painful emphasis: Where will he commence his labor? Shall it be in city or country, north, south, east or west, on land or sea? It is a question which may prove of the

highest moment as regards all the objects which the young physician proposes to himself, and will doubtless cause him some anxious days and sleepless nights.

I do not propose to answer that question for him, but only mention it as one of his opening perplexities; and he himself, consulting his own tastes, balancing the interests and influence which he can bring to bear in this place and in that, the number of regular and irregular practitioners with whom he must compete here and there, and the thousand other *pros* and *cons* which he supposes may influence his success, will decide, and generally he will decide for the best.

Being at length located in the place of his choice, the first matter which he will be likely to observe as operating to his disadvantage, is his lack of experience and age.

The fact of being a young man was, in times past, a sufficient barrier to present success in any profession; and to be a young physician, especially, was a crime which it required a multitude of atoning virtues to outweigh. So true was this as to give rise to the proverb, "a physician cannot earn his bread till he has not teeth to eat it." It is true that our present high-pressure principle of bringing things to pass, and the lack of veneration, or even respect, which too much characterizes our nineteenth century, has to some extent removed this barrier, and yet it is a barrier, and one which operates more to the disadvantage of the young man, attempting to gain a foothold in the medical profession, than in almost any other situation. Nor need we be surprised at this. Life and health are each individual's own most valued treasures, and however much he may ad-

Reprinted from the Communications of the Rhode Island Medical Society, Volume 1, pp. 85-96, 1877.

Our readers may be interested in this glimpse of concerns facing the medical profession during the Civil War era — the struggle to develop a positive relationship between the public and physicians.

mire the general talent and bearing of the young practitioner, still, when these most cherished treasures are in peril, we cannot with any justice censure him if he chooses to commit them to the keeping of more experienced hands.

This is an obstacle to the young man's progress which is inevitable, which he must expect, and which need not discourage him, for confidence such as he desires, and such as is worthy of the name, is a plant of slow growth, and it may be that for him such can only be reared and nurtured, by ministering at first with patient hand and genial heart at the bedside of poverty, not in tardy response to oft-repeated importunities, but willingly and unsolicited, seeking the abode of suffering and want, and administering the cordial of kindness as well as the other resources of his art; and the young physician whose kindness of heart, independent of personal interest, would not prompt him to such acts of humanity, is not worthy of the profession which he has chosen, and whose honor he tarnishes. On the other hand, the young physician who has the poor amongst his warmest friends, may not only experience the pleasure which springs from the consciousness of having done a kind act, but he may also, without presumption, cherish the expectation of ultimate success and honor.

I do not wish to drag up to public gaze the foibles and failings of the profession which so many of us here present have chosen and love, but will only softly whisper a rumor which has reached my ears, as it doubtless has yours also, that there is already in the field a large and oftentimes extremely worthy class of practitioners, who have not yet reached that measure of success which was the utmost boundary of their hopes, and that the love wherewith these brethren do love a younger than they who may chance to come among them, is not exceedingly great, and that any error, however small, which he might chance to make in the *diagnosis* or treatment of his first important case, would not be covered with so thick a mantle of charity as would serve to hide it from the gaze of a harshly judging world, but on the contrary, by some mysterious means, this same slight and harmless error, (which, after all, might not have been an error but something *new*), soon comes to the gaze of this same harshly and ignorantly judging world, not only divested of that comely mantle, but even so magnified and distorted that nobody acquainted with the facts would ever suspect its origin.

And furthermore, it has been reported that

should this new comer have occasion to call in council one of the loving brethren, even though the case should terminate with the most gratifying success, yet at the next illness in that family, from some inexplicable cause, *his* services are not required, but those of the senior instead. It is very strange, but people have a perfect right to call whatever physician they choose, of course; and now he thinks of it, can it be that that wise, mysterious look which was given him while that consulting brother was speaking, (as he had no right to do, in an under tone), with the "lady of the house," had anything to do with this result? Possibly not; and yet in his own mind he has reached the wise conclusion that a little vigilance on his part can do no possible harm the next time he has to call for consultation. For my own part, I place but little confidence in these scandalous reports. Nevertheless, true it is, that physicians are human, even accepting the old woman's classification of the species into men, women and doctors, and, in common with the rest of our frail humanity, possess the instinct of self-preservation, if not of positive selfishness; and having this common instinct, they respond to it just like other men, as ministers, lawyers, hack-drivers and rag-pickers. That is, if a new man too nearly of the same sort comes among them, making, as they think, one too many, they proceed to use their *most persuasive arguments* to put him out. But that doctors are especially unkind in this respect, we have yet to learn.

But now, having overcome the disadvantages incident to the very commencement of professional life, having by skill and kindness secured confidence and esteem in the community, and by diligence, independence, and that most potent of all means, minding his own business, succeeded in stopping the mouths and defeating the machinations of unfair competitors, the young physician has established himself in a pleasant and remunerative practice, rejoicing in the thought that his time and toil and anxiety have not all been squandered for naught, and in the pleasing hope of future success and usefulness. But here, again, he is doomed to chagrin and disappointment, in beholding many of his firmest friends and most reliable patrons, from all grades of society, drawn, as if by irresistible magic, after the first form of delusion and empiricism which happens to be offered them. The Indian doctor makes his appearance in the quiet village; extensive rooms are opened on the opposite side of the street, and well supplied with all the appliances of his trade; innumerable roots and herbs

of known and unknown name, unguents of unheard-of potency, plasters to soothe all pains and heal all wounds, and holding such enmity to the dreaded cancer, as to drag it, root and branch, even to its utmost cells and fibres, from the system of the believing patient, no more to find lodgment there nor taint the peaceful current of his now renovated blood; powders, composed of stings and fangs of serpents, entrails of toads and eyes of fishes, compounded by a seventh son, while the clock was striking the mysterious hour of midnight, and possessing virtues which no ill that flesh is heir to can withstand; and if charms and amulets are wanted, he can say, like Shylock of his balances, "*I have them ready*"; hand-bills are spread around, relating his wondrous deeds of cure, well certified by distinguished foreigners, literary men of note, and clergymen, and as he himself, in fanciful attire, with brisk tandem team, dashes with Jehu-speed from point to point, the whole town pauses and stands agape with wonder and admiration. A delightful sensation of something new and strange steals over the community, and soon the Indian doctor's rooms are crowded with deluded patients, to whom hope and excitement lend temporary relief, and our intelligent and worthy practitioner sits quietly in his office, forgotten and perhaps dispirited.

Or if this *omnium gatherum* of a doctor is obliged to content himself with the rabble, and fails to draw off the more refined and fashionable portion of the practice, *they* are only reserved for a more refined and exquisite delusion. Our young friend soon discovers amongst his former patrons, ten fashionable women, with a set of indescribable symptoms, and one middle-aged man of literary occupation and sedentary habits, taking more buckwheat cakes and sausages than exercise, who have ceased to employ him, and have become thoroughly convinced that those tiny globules, saturated with the 100th dilution of *mercurius dulcis*, or better still, the *dulcamara*, (sweet names), have greater potency for the relief of their peculiar ills than all the advice and medicines which it has been their fortune to obtain, and notwithstanding those cases in which the patients died with all the symptoms of poisoning, in consequence of the fearful potency imparted to the medicines by numerous dilutions, still disciples to the faith were multiplied, and for a time, friends to encourage the intelligent physician, were few.

These "quack doctors" are a motley body, comprising every kind of specialty: Steam doctors, worm doctors, natural bonesetters, corn-doctors,

water-casters, astrologers, herbalists, "wise men," witch-finders, and curers of syphilis and diseases of the sexual organs, who are professed poisoners and procurers of abortion, with hardly an exception, a group of scoundrels. The ranks of the quacks are also swelled by outcasts from the legitimate profession, men who are excommunicated, either because of their vices or of their follies, and who have been morally punished by a rightful deprivation of professional intercourse with their brethren.

In another class are comprised country clergymen, ladies having a taste for medicine, persons in private station with a smattering of knowledge, but especially the retailers and compounders of drugs, and professed nurses. None will lack followers, and in proportion to their impudence and mysteriousness will be their success.

Alas! for poor human nature. Disease, suffering, disappointment and despair will grasp at a sun-beam, or cling to a shadow. The sufferer who seeks relief of the charlatan, when his fate has been pronounced by the legitimate practitioner, is to be pitied more than blamed. The reprehensible parties are the friends of the sufferer who permit, and the missionaries of the quack who spread, the delusion. It has been well said, the public mind must be amused, and while the masses are engrossed with war or politics, particular classes in certain localities find relief to certain innate promptings or cravings in outbursts of theomania, revivals or miracles of any description, while the sickly and distempered eagerly rush after every novelty which offers.

When argument, reason, a reference to pathology, common sense, or experience, are tried in discussing the question of one of these cures, no matter how performed, the answer thrown in your teeth, along with a plentiful garnishing of epithets about "professional obstinacy," "wedded to old opinions," "incredulity," &c., is: There is the simple fact; the patient is cured after the most eminent of the faculty had given the case up, sent the person away to die, and would not give him even the chance of an operation.

If any one inquire what good or harm these medical quackeries do, we answer they are deceptions, proving either want of knowledge, or want of honesty, or both, in their promoters. Yet there is money to be made of them, and *that* their upholders know full well.

A cure for a heretofore incurable disease is promulgated; a book is written on the subject, the public press is invoked, and not in vain; with-

out any attempt at dishonesty, or the slightest idea that they are gulled, an editor or two, influenced for humanity's sake by a philanthropic friend, is induced to introduce a well worded paragraph about the cure; it is then public property, and no matter how absurd or incredible it may appear, it is copied from periodical to periodical; it is cut out of newspapers, and sent in rose-colored envelopes from one lady to another, and so the reputation is established, and patients, with anything at all resembling the disease, flock in hundreds to the discoverer.

It is true he does not cure them; perhaps he does not know which are curable and which are not, for diagnosis does not come by instinct. He may not be, and in all probability is not, a pathologist. His panacea, or, if he is a knowing man, his remedies, are applied to all comers; and some get well, but not those affected with the incurable disease. The object, however, is attained, notoriety is achieved, patients are caught, and the remedy is only subsequently resorted to in special instances.

Nothing pleases a certain class of patients so much as to be talked about — to think that their disease is in any way peculiar. They are elevated from the martyr into the hero; they boast to you that the new doctor said, in the words of Brennon, that their case was "*The worse he ever saw, save one.*" Even though they are no better, they become the fast friends and most indefatigable missionaries of the new system and its professor.

If you meet one of them, and ask, "Is he really cured," the answer is "Well, I can't say I am much better, but that is because I did not go soon enough," or "try the system long enough"; "circumstances prevented my remaining any longer under treatment," &c., &c.

These are not fancy sketches. Who is there in extensive practice who has not encountered such people, and observed such conduct? The pertinacity with which the patient and his friends, — when they have thrown overboard the old family attendant; the kind, skillful, generous, judicious friend of years, for the quack, or for quackery of any description, — will try to persuade you that they are cured, would be amusing if it were not so lamentable. They will lose their temper with you if you hint that they are no better than they were, and attribute to the "well-known prejudices and illiberality of the profession" your reminding them of the opinion you gave some years before they had sent a lock of hair in a silk bag to a madam or mademoiselle to supply them with

a pathological horoscope on the state of their liver or stomach.

So seductive and apparently irresistible is the charm which mystery lends to every object upon which her shadow falls; her grounds are all enchanted grounds, and no sooner does the visitor pass their pleasing confines, than Reason seeks a shady nook for dreamy slumber, and fancy plumes her wings for flight. Reason now dreams of the accomplishment of all his pet projects! — long marches over hitherto unexplored and impassable ways — lofty summits reached, and long lines of truth explored and frowning citadels, so long impregnable, now proudly stormed and occupied. Fancy the meanwhile humoring all his whims furnishes materials for his gigantic schemes! With busy hand and grotesque flight she circles round, dropping, just at the right time and spot, huge grappling hooks of sand to root up century-grown oaks; ropes of air by which to scale lofty precipices; bridges made with beams of moonshine to make easy passage over impassable chasms; and bombast, instead of bombshells, for ammunition wherewith to battle down the castle walls of stubborn error; and all the time that Fancy is playing such tricks, poor sleeping Reason lies and smiles and nods approvingly at her, as she furnishes each useless aid, like a jolly automaton in the shop window, nodding and smiling at each passer-by.

"In faith, 't is strange, 't is passing strange — 't is pitiful, 't is wondrous pitiful," that men and women will so suffer the reason to be befogged and fooled by Fancy, as to make the greatest nonsense appear the soundest sense, and allow themselves to be tickled and deceived by phantasms, until nothing is true unless so subtle as to be incapable of proof, and nothing real unless so refined as to escape detection by the most perfect sense, and the more ridiculous the conceit, the more exquisite the sensation of being fooled into a belief in its reality.

As for the reasons for this mania after the new and ridiculous in medicine, there is neither time nor necessity to give them here. Suffice it to say, that they arise from three principal sources:

First — The blunders, and too often the lack of knowledge, among regular practitioners.

Second — The ignorance which prevails in the community concerning the structure and functions of the body, as well as what ought really to be expected from medicines.

Third — The false promises and impudence of quacks.

What then shall the intelligent physician do? Shall he reason? Reason is in mystery's domain listening to fancy or imagination. Could he convince the Indian that his priest or medicine-man could not by his charms expel the bad spirit that was causing him pain? Could he convince the crowds who sought the royal touch of Charles the Second, that that touch would not bring healing? Could he persuade the dupes of Perkins' tractors that their pains would not be withdrawn? Could he persuade the millions who have given their money to build palaces for Brandreth, Townsend, Moffat and Sherman, that it would have been better had the nostrums of all these empirics become physic for sharks instead of men? Then might he hope to break by argument the hold which the present race of charlatans, dream-mongers and *actual rascals* in medicine, have upon the minds of this wonder-seeking and gullible generation.

No! It is only by diffusing knowledge that such false ideas can be removed. Men study mathematics, and Latin, and logic, and get a smattering of knowledge about things in the heavens above, the earth beneath, and the waters under the earth, but when asked anything about the structure and furnishing of the house they live in, — that most wonderful of the Creator's works, — the human body, they are most profoundly ignorant. The skin is only a nerveless outside covering to keep the rest of the body from smarting.

A pitcher *sweats* as well as a man, and it certainly has no *pores* to be attended to; therefore soap and water are useless articles except in cases of *visible dirt*. As for that which is taken cognizance of by *another sense*, Lubin's extracts furnish the only civilized method of obviating it.

The stomach and lungs are transposed in *place* if not in *function*, and the *poor old liver* occupies at least two stories in this castle of ignorance.

How is it to be supposed that when there is such mystery as regards the structure of a machine, there will not be mystery as regards what is necessary for its repair. Here, then, is work to do, and shall the physician sit idle in his office watching for one more patient, and dreaming of that sweet time when the river will have run past, and the world returned to the good old days which history records and prophets sing? If so, of one thing he may be assured, that if that time should come, there would be no use for him — he would be entirely behind the age.

No! The idea that the physician's business is to cure, and keep people as ignorant as possible

of how he does it, is all folly, and worthy only of the days of alchemy and magic.

The physician has one department of the world's education committed to him, and shamefully has he neglected it, and bitterly to-day is he reaping the reward of his neglect. Let him then comprehend the full import of his mission, and learn to instruct while he applies his art, if he would see his profession returned from the hands of charlatans and mercenaries, and wearing that honor which is so justly its due.

But, in view of all the difficulties to be encountered, inexperience, coldness, not to say hostility, of jealous brethren, false ideas in the community, and the cold pretensions of irresponsible empirics — what knowledge, what honesty, what zeal, what firmness, what high personal and professional honor, are necessary to carry the young man safely through the first few years of professional life, and keep him from yielding to those seductive influences which would lead him to fall in with the current on which he sees many borne past towards the one great object of their lives, the acquisition of wealth.

Surely wealth is not to be despised, and none of us expect to give a life of labor for naught. No man in any station in life, no statesman, no lawyer, no physician, no clergyman, no soldier, gives his labor, mental or bodily, to society "without hire," but the degrading of a noble profession to the mere matter of getting so many dollars and cents, and seeing how much one can make out of the profession, and how small returns he can make to it, is simply the pure, double-refined extract of meanness and dishonesty, and the man who would be guilty of it, should be pricked in the ear, or branded upon the cheek, that he might be known, and shunned, and despised, everywhere and by every noble-minded man. Wealth in any profession, if acquired at all, or at least honestly, by rendering to society an equivalent, must follow an able and honest discharge of the duties of that profession.

But, gentleman, the objects of our profession are more noble than material wealth in any form. They are to drive away ignorance and mystery, by causing truth to shine out broad-cast, spreading a knowledge of God's most beautiful and perfect works, as they appear in those studies which minister to our art; to lengthen out and render tolerable — nay, even enjoyable — lives which disease of body and mind had conspired to render comfortless and to destroy; to minister at the bedside of pain and languishing, giving quiet to the pain-racked body, and strength and comfort

to the faltering mind; to wipe the cold damps from the brow, while Death prepares his dart, and point the departing soul to the life which knows no dying.

And these are objects which neither cold-hearted selfishness, nor avarice, nor coarse vulgarity, nor stupid ignorance, can ever rise to appreciate, nor have heart or courage to accomplish. It is only the brave, the honest, the sympathising, the self-sacrificing, who dare truly to undertake such labors; labors such as Cicero declares "bring men nearest to the gods."

Such objects and such labors we, if worthy of our calling, have undertaken, and God helping, we will accomplish them; nor will they be without enjoyment, for what enjoyment can exceed the luxury of overflowing gratitude fresh from the heart and lips of those whom skill and tenderness have snatched from suffering and anguish, and perchance from death; these with the joys which spring from ever increasing knowledge are our pleasures, and they are such, it seems to me, as Cicero might add come nearest to the pleasures of the gods.

And, in conclusion, I will only add my own best wishes for each member of this society and of the profession, that the blessings which they seek to preserve for others may be enjoyed in fullness by themselves; that friendships, without which earth is but a wilderness, may spring up in freshness to gladden all the pathway of life; that well earned honors may be the chaplets which shall bind their brows in age, and that an unclouded reason, pleasant memories and the Christian's hope may cheer each in the hour of death.



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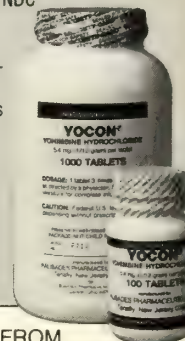
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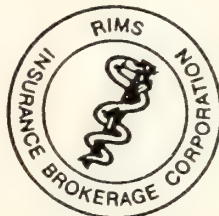
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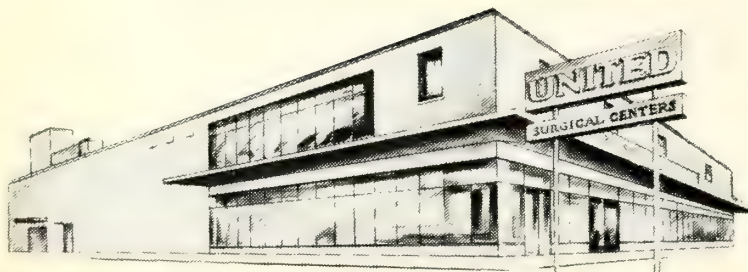
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Epidemics, Society, and History

The Conquest of Epidemics is a Result of Complex Historical Forces

Naomi Rogers, PhD

Recently, historians of medicine have been called upon more frequently than ever to reflect on the lessons that the history of disease can bring to present experience. The acquired immune deficiency syndrome (AIDS) crisis has brought into sharp focus the significance of the ways society defines contagion. These definitions directly influence the direction of research and public health policy: who spreads infection, who is seen as dangerous, how the sick and those suspected of carrying infection should be identified and treated. Health professionals and the public have both turned to the laboratory, hoping that the discovery of a vaccine will solve the social and medical complexities of the epidemic.

But our current experience has also reminded us that epidemic disease is far more than simply a biological phenomenon. Disease, clearly, has social, political, economic, and moral dimensions. AIDS reminds us of the consistent role of fear and hysteria, the stigmatization of marginal groups, and the tensions between guarding the public health and ensuring civil rights. Further, as historians have recently warned, we should not expect a vaccine or a cure to make these other complicating aspects disappear, especially, as Allan Brandt has argued, when dealing with the problems raised by a disease linked with issues of sexuality and morality.¹ Historical analysis suggests that understanding the role science plays

in defining contagion and determining medical and social responses to an epidemic are problematic even for nonvenereal diseases.

In this essay I examine three examples from the historical record: the bubonic plague in medieval Europe, cholera in nineteenth-century America, and smallpox since Edward Jenner's discovery of the vaccine. Some recent observers have suggested that AIDS has seemed particularly frightening because our recollection of experiences of epidemic diseases of the past has faded so quickly and so much of the attendant terror is now forgotten, but in fact, epidemics are part of our everyday vocabulary. We use medical metaphors for a variety of non-biological topics and speak of epidemics of crime and teenage pregnancy. Perhaps these biological metaphors offer us hope for victory over otherwise seemingly intractable social and economic problems. Yet, diseases such as syphilis, cancer, and heart disease are still with us, and others seemed to have appeared from nowhere. Science, history has shown, brings ambiguous answers and makes our search for more magic bullets both precarious and poignant. A recent historian has argued, indeed, that "the meaning of disease has in the recent past become more rather than less ambiguous."²

Our experience with AIDS has heightened our awareness of the social meanings of an epidemic, the lasting association between dirt and disease, and the sanctions imposed on those groups believed to be spreading infection or at risk. Defining and assigning responsibility is an essential element in making sense of an epidemic, and the

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role of science and scientists in determining that element remains limited. Medical historians have long argued that, in order to explain the meaning of epidemics, we must examine their social and cultural context. Research and public-health policy are influenced by the way contagion is defined, how the source of danger and infection is understood. From a scientific standpoint, the source of contagion is an objective physical agent, such a germ or virus. But the study of varying theories of contagion in the past complicates this straightforward biomedical perspective.

Our parents and grandparents believed that disease could be spread by bad air and putrefying matter or by unsanitary and immoral habits. A belief that filth, be it physical or moral, is the source, even the cause, of disease still lingers today. Anthropologist Mary Douglas has argued that who and what are defined as unclean may be both culturally significant and relative.³ Thus, the definition of filth is part of our historical context; those most feared are often marginal groups, in the past including Jews, immigrants, prostitutes, and the poor. In this analysis of aspects of the history of plague, cholera, and smallpox, I hope to tease out the links between contagion and responsibility, and the controversial role scientific solutions have played.

Plague

One of the most influential studies of epidemics in the past has been the history of plague, particularly the Black Death of the Middle Ages. The bubonic plague (caused by the bacillus *Yersinia pestis* and spread by fleas carried usually by the black rat) originated in Central Asia where the wild rodents of the steppes constituted a reservoir of infection. In the early 1300s the disease began to spread to the Black Sea and then on shipboard to Constantinople, Venice and other European port cities. By 1350 all of Europe from Russia to Spain was infested with the plague, and it was devastating. At least a quarter of Europe's population died; whole villages disappeared; England and France agreed to abandon the war they were engaged in; unmanned ships drifted on the Mediterranean and North Seas as their crews were entirely wiped out; and in southern France deaths were so common that the Pope consecrated the river Rhone at Avignon so that corpses flung into the river might be considered to have had a Christian burial.⁴

The medieval public immediately began to ask: who is to blame? They sought culprits and found them, as communities have done consistently

through time, in strangers, the poor, and other marginal groups. As historian Ann Carmichael has shown, the Black Death, for example, intensified the medieval Christian notion of the scapegoat Jew. Jews were suspected of purposely spreading plague by contaminating wells or by anointing houses and individuals with an imagined plague poison; and they were persecuted accordingly. At Freiburg all known Jews were hoarded into a large wooden building and burned to death. At Strassburg over two thousand were hanged on a scaffold set up in the Jewish cemetery.⁵

Public officials, similarly, focused their attention on these special groups in order to try to guard the public health. Authorities in Northern Italy enacted legislation which would mark groups believed suspect in a way everyone could see. Significantly, officials chose the color yellow, a color traditionally used to identify criminals and lepers. The groups thus marked — prostitutes, Jews, foreigners, and the poor — were seen as sources of disorder and danger. Jews were required by law to wear a large yellow Star of David on their caps or coats. Prostitutes were also labeled in yellow and, in one instance a member of a male homosexual couple was dressed in yellow and forced to witness the gruesome execution of his lover.⁶ The experience of bubonic plague intensified a fear of groups already marginal, and the concept of contagion provided the justification for their persecution.*

Cholera

The tendency to victimize and thereby somehow hope to control a frightening epidemic did not disappear with the decline of medieval Europe. The American experience with cholera epidemics, as historian Charles Rosenberg has shown, similarly involves popular assumptions about the close connections between marginality, filth, and disease. From the early 1800s first Europe and then America began to suffer increasing outbreaks of cholera. Cholera (a disease spread by water or food contaminated by feces infected with the comma-shaped bacterium *Vibrio cholerae*) is a swift and deadly disease. It can cause a victim walking along the street to fall over suddenly, body dehydrated, face jaundiced and sunken, dead. The disease was linked in the popular and medical minds with filth and poverty, urbanization, and immigration. Cholera epidemics, after

*Hans Zinsser's classic *Rats, Lice and History* (Boston 1925), was a graphic exposition of the impact of epidemics on history. ED.

all, appeared consistently in the worst slums of the crowded cities of the industrializing Western world.

Many Americans believed that cholera had appeared to punish a nation mired in materialism and sin. In 1849 during a devastating national epidemic President Zachary Taylor recommended a day of national prayer and fasting.⁷ In fact, the poor and immigrants were frequent victims. More than forty per cent of those who died from cholera in New York City were Irish, and the cities with the greatest immigrant populations — New York, Cincinnati, New Orleans, St. Louis — suffered most severely. White Protestant Americans blamed the epidemic on immigrants flooding these cities with their heathen and unsanitary habits. One New Yorker wrote in his diary in June 1849 that immigrants were “filthy, intemperate, unused to the comforts of life, and regardless of its proprieties . . . [they] flock to the populous towns . . . with disease engendered on Shipboard, and increased by bad habits on shore, they [infect] . . . the inhabitants of these beautiful Cities, and every paper we open is only a record of premature mortality.”⁸

The conquest of cholera was finally achieved through sanitary measures based on the filth theory of disease, not through bacteriological intervention. In 1854, John Snow (1813-1858), an English physician, demonstrated that the disease was transmitted by contaminated water. His work was part of a broader movement on both sides of the Atlantic to improve city life and the conditions of the poor through environmental public health reforms. Municipalities began to introduce effective sewage systems, housing regulations, and other sanitary reforms. By 1883, when German bacteriologist Robert Koch first identified cholera's specific etiological agent, epidemic cholera in America was already a disease of the past. New York City, for example, which had seen over five thousand deaths in the 1849 epidemic, had established the nation's first Metropolitan Board of Health to deal with the next major outbreak in 1866, and the Board's sanitary measures were so effective that the city had fewer than six hundred deaths.⁹

Certainly, the development of the germ theory enabled physicians and public officials to deal more effectively and precisely with their communities' health problems. Bacteriological investigators, such as Louis Pasteur, Robert Koch, and Emil Behring, not only identified the specific etiologies of a growing number of diseases, but

developed methods to help physicians diagnose and treat them. A great hope for the prevention of disease was the development of the field of immunology. One of the most dramatic therapies was the discovery in 1891 of diphtheria antitoxin, which effectively saved thousands of children's lives. Also, Louis Pasteur used bacteriological techniques to develop a vaccine against rabies, and other researchers followed with vaccines against cholera, typhoid, and plague. Physicians and scientists in this heady period of bacteriological successes hoped that the further pursuit of etiological solutions, based firmly on laboratory research, would provide more precise and effective methods to conquer the world's ills. But their searches for magic bullets were only partially successful.

Smallpox

Consider one of the most famous examples in medical history: the development of the smallpox vaccine. This vaccine, now acknowledged as an important basis for the development of modern immunology, was, in fact, not based on an etiological theory at all.¹⁰ Smallpox (a highly infectious viral disease spread by not only the lymphs and pus, but also the scabs of the pocks themselves) was a major cause of death, blindness, and disfigurement. In Europe during the seventeenth century perhaps one in every ten people died of the disease.¹¹ At that time it was clear that smallpox was spread by personal contact, but by 1800 the notion of contagion was an old-fashioned medieval idea. Most nineteenth-century doctors believed that diseases were not specific, but the result of a general imbalance between the body and the environment. Only quacks tried to cure a disease with a single specific remedy. Smallpox was thus, in elite medical theory, an exception and anomaly.

The development of immunological techniques to prevent smallpox has a history fraught with social, political, and even moral conflicts. The introduction of inoculation to Western communities is a case in point. An understanding of smallpox immunity was already prevalent in Africa and Asia. Chinese doctors, for example, blew pulverized smallpox scabs into the noses of their patients.¹²

Anesimus, an African slave, introduced the knowledge of inoculation (whereby the pus or scab from a smallpox victim is inserted under the skin of a healthy person to cause a mild outbreak and produce immunity) to his owner, the New England minister Cotton Mather. Mather, at the

start of a smallpox epidemic in 1721, convinced a Boston doctor, Zabdiel Boylston to inoculate first his own family and slaves, and then some of his neighbors. Local physicians and other members of the community opposed his actions, and Mather even had a grenade thrown into his house. Boston doctors such as William Douglass argued, with some justification, that this medical innovation was dangerous, for the amount and virulence of the smallpox poison could not be controlled, and it might even spread the disease rather than prevent it. Further, some were suspicious of a science that seemed irreligious and violated the moral law of God, while others noted that slave merchants hoped to benefit significantly by the ability to prevent their charges from dying of the disease.¹³

A rural English physician, Edward Jenner (1749-1823) was the first to develop and popularize the smallpox vaccine among the medical community of the West. Jenner first vaccinated (a word he coined from the Latin "vaccinia" meaning from a cow) a child with cowpox on May 14, 1796. He took pus from a cowpox ulcer on the wrist of a local dairy maid, Sarah Nelmes, and inserted the material under the skin of an eight-year-old boy, James Phipps. Jenner believed that a mild case of cowpox would prevent the more deadly appearance of smallpox, an idea drawn from a popular tradition among farmers and dairymaids in rural England. Two months later he inoculated the boy Phipps and found no reaction to the deadly disease — the vaccine worked.¹⁴

Soon, news of the Jenner vaccine had crossed the Atlantic. Benjamin Waterhouse (1754-1846), a Rhode Island-born physician, was one of the first in America to send for the vaccine and popularize it among his colleagues. In July 1800 Waterhouse performed the first vaccination in America, on his son, and encouraged the Boston authorities to conduct a public experiment, which was successful. He also sent a pamphlet and a list of his cases to then Vice President Thomas Jefferson. Jefferson enthusiastically had his own family vaccinated, and in 1801 as President wrote to Jenner: "Yours is the comfortable reflection that mankind can never forget that you have lived; future generations will know by history only that the loathsome smallpox existed."¹⁵

Jefferson was too optimistic; the public acceptance of his vaccine was not so easy. During the nineteenth century, some European countries did make vaccination compulsory: Denmark in 1810, Prussia in 1835, England in 1853. But

in the United States it was not through federal policy, but the choice of individual communities that vaccination was introduced. With the expansion of American elementary and secondary education after the Civil War, and the compulsory attendance of young children, public officials found that one of the most effective ways of enforcing vaccination was to bar any child from attending public school without proof of vaccination, usually a scar.¹⁶

Some Americans, however, believed that compulsory vaccination was dangerous, ineffective, and a violation of their civil rights. In the late nineteenth century resisters formed influential Anti-Vaccination societies, and tried to influence public-health policy. Even with the popular and medical acceptance of the germ theory of disease, and the idea that specific diseases should be treated by specific remedies, many communities remained suspicious of this medical technique.

The strength of this resistance can be seen in the example of Milwaukee, in the 1890s a rapidly industrializing Midwestern city, and the home of increasing numbers of German and Polish immigrants who lived in the poorer sections of the city's South Side. As historian Judith Leavitt has shown, immigrant resistance to public-health policy during a smallpox epidemic in 1894 decreased the powers of the city's public-health department. The department pursued strict and culturally insensitive policies during the epidemic, including removing children believed infected from their homes to the city's Isolation Hospital, and a widespread vaccination campaign. Members of the city's immigrant communities were outraged at what they believed was an attack on their civil rights and immigrant cultures.

Many rejected the whole idea of vaccination, seen as the injection of a poison into the body, or that a child could be better cared for in a hospital than at home. They were quick to point out that if the city's smallpox hospital was safe, then why was it built in the heart of the South Side? When a Health Department ambulance came to collect a child reported to have the disease, angry neighbors threw stones and scalding water at the ambulance horses, and women threatened the guards with "baseball bats, potato mashers, clubs, bed slats . . . and butcher knives." The ambulance retreated.¹⁷ By the end of the epidemic, which did rage more fiercely in the South Side, the city's health commissioner had been impeached and the department lost some of its police powers, which it never regained.

Popular suspicion of compulsory vaccination lingered. In fact, in 1896 on the hundredth anniversary of Jenner's first vaccination attempt, the English county of Gloucestershire, where he had practised, experienced its most severe epidemic of smallpox. As late as 1930, the United States reported forty-eight thousand smallpox cases. But by 1980 the World Health Organization (WHO) announced that smallpox had been eradicated.¹⁸ It was an uphill battle, for the success came only after the organization's third international attempt. Still, the results of WHO's campaign can be judged by the fact that few of the students who graduated from college in 1988, unlike most of their parents and teachers, have smallpox scars on their arms.

Social and Moral Factors

Our definition of disease today is a combination of our historical experience and a shifting sense of what can be investigated and achieved through laboratory research. The successes that scientific research has brought, particularly with diseases such as diphtheria and poliomyelitis, has left us with a faith in immunological therapy. But the past also suggests that the way to deal with epidemics such as plague, cholera, and smallpox may go beyond an etiologic approach. These diseases have not been conquered through biomedical fixes alone. The history of disease is intimately bound up with social and moral factors — groups seen as marginal, cultural beliefs, the fear of individuals and communities, the question of civil rights. AIDS is clearly, though not only, a "social disease," a disease with social and moral as well as biological dimensions. Some recent commentators have seen AIDS as a judgment on the sexual promiscuity of modern life, and reinterpreted homosexuality as itself a virus invading schools, homes, and the community at large. These fears and associations will not simply disappear with the development of more precise etiological tests and therapies. AIDS, I would suggest, will be most fruitfully conquered when these diverse and at times contradictory aspects of what makes up a disease are integrated into public health and research policy.

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The author would like to thank Irving Beck, Joan Richards and John Harley Warner for their comments and encouragement.



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REVIEW

Therapeutic Endoscopy of the Biliary Tract

Techniques Have Been Developed for Management of a Wide Variety of Problems

Edward R. Feller, MD

Endoscopic retrograde cholangiopancreatography (ERCP) involving duodenoscopy with cannulation of the ampulla of Vater and injection of contrast dye into the pancreatic and biliary ducts has widespread use in the diagnosis of pancreatic and biliary disorders. In recent years endoscopic techniques have been developed facilitating effective non-operative management of a wide variety of problems including common bile duct stones, benign biliary strictures and malignant strictures of the biliary tract. This review outlines the scope and nature of endoscopic treatment of biliary disease.

Endoscopic Sphincterotomy

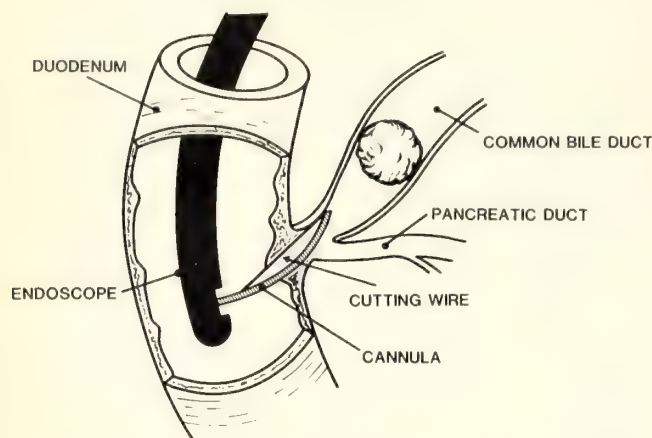
Retained or recurrent common bile duct stones after cholecystectomy occur in five to ten per cent of patients in large series.^{1,2} Endoscopic sphincterotomy (ES) compares favorably with operative management for gravely ill, elderly and other high risk individuals with common bile duct stones after cholecystectomy. This technique involves direct per-oral cholangiography via a lateral viewing endoscope utilizing a wire-containing cannula through which electrocautery current is applied.³ Once stones are documented by direct dye injection using a cannula, the electrified wire-containing papillotome is placed in the duct. After

confirming position of the wire fluoroscopically, current is applied and a controlled incision is made, transecting the intra-mural sphincter (Fig 1). An incision of 0.5 to 1.5 centimeters is made depending on configuration of the ampulla and the size of the stone. Most stones less than one centimeter in diameter pass spontaneously; larger calculi may need to be extracted via a balloon-tipped catheter passed above the stone, inflated, and then withdrawn. Success rates in large series range from 85 to 90 per cent with a 5 to 10 per cent complication rate including pancreatitis, cholangitis, duodenal perforation, and bleeding.⁴ Procedure related mortality is in the range of one per cent. The major technical problem limiting success involves very large stones which cannot be extracted endoscopically. Contraindications to ES include severe coagulation defects, long stricture of the common bile duct for which the risk of perforation is high, and uncertainty of perampullary anatomy precluding proper sphincterotomy positioning.

Indications for endoscopic sphincterotomy have been extended to include common-bile-duct stones with the gallbladder *in situ* in high-risk patients. Collected series suggest that the risk of future cholecystectomy for recurrent biliary stones is 10 to 15 per cent with a mean follow-up of 1 to 6 years.⁵⁻⁷ In a large retrospective series of 1272 patients from several centers, 108 of 1272 patients required cholecystectomy within three years of ES because of recurrent biliary symp-

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Fig 1. The ampulla with sphincterotome wire in position prior to endoscopic sphincterotomy.



toms.⁵ Most recurrent problems occur in patients having stones in the gallbladder at the time of sphincterotomy or a non-filling gallbladder with dye injection via ERCP. Other indications for ES (Table 1) include ampullary stenosis, dyskinesia of the bile duct, and dyskinesia of the sphincter of Oddi, ES is also indicated in post cholecystectomy patients with a T-tube in place in whom percutaneous extraction has failed or in whom a delay to allow the tract to mature is not appropriate clinically. It is also indicated in occasional patients with a malignant ampullary tumor to provide relief of jaundice by enlarging the ampullary orifice.

Early experience with diagnostic ERCP suggested a high complication rate when the procedure was done early in the course of acute inflammation in patients with pancreatitis. However, recent studies in severe pancreatitis suggests that urgent ERCP performed within 48 hours of onset of an attack in patients at high risk for having common-duct stones may identify a group in whom sphincterotomy and removal of impacted stones may affect the clinical course beneficially.⁸ In a recent controlled trial of urgent sphincterotomy versus consecutive treat-

ment for acute gallstone pancreatitis, there were fewer complications in the 59 patients who underwent ERCP ES than among the 63 treated conventionally.⁹ Hospital stay was also shorter for the endoscopically-treated group. The difficulty lies in selecting patients with acute pancreatitis who would benefit from urgent biliary decompression and determining whether such an aggressive approach contributes to decreased morbidity and mortality.

Nasobiliary Catheters (NBC)

Temporary decompression of the biliary tract may be accomplished by placing a NBC above a common-bile-duct stone or biliary stricture. NBCs are long polyethylene tubes one end of which is positioned inside the biliary tract while the other end exits through the duodenum and out the nostril with connection to a biliary drainage bag.¹⁰ If endoscopic sphincterotomy is unsuccessful in clearing the bile duct of stones, an NBC may be placed to reduce the risk of stone impaction at the ampulla and maintain biliary drainage. This maneuver prevents impaction while the feasibility of further attempts at stone extraction are assessed either by extending the sphincterotomy incision at a later date or by a surgical approach. In addition, NBC provides access for perfusion of the duct with a stone dissolving agent such as monooctanoic acid. This agent has a success rate of 30 to 40 per cent over an interval of 7 to 14 days in stone dissolution.¹¹ NBCs have also been utilized for preoperative decompression in patients with extrahepatic biliary obstruction prior to surgery, as well as to allow access for intraluminal radiation therapy in malignant tumors of the bile duct.

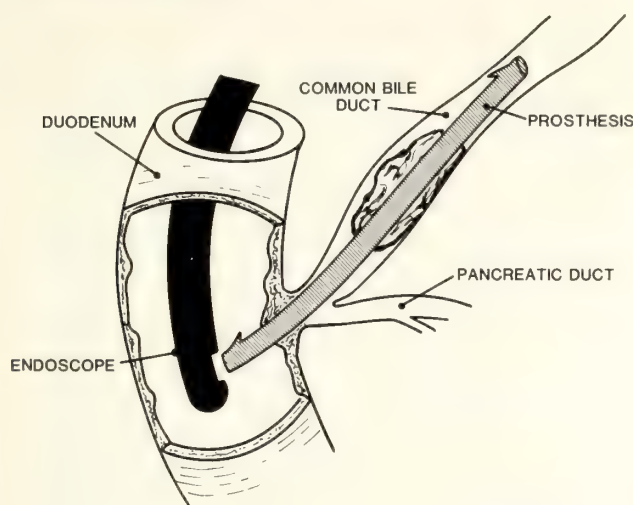
Biliary Endoprosthesis

The one year survival rate of pancreatic cancer is 10 to 20 per cent in large series.¹² Forty to 70 per cent of these patients will develop obstructive jaundice. Stents or endoprostheses placed endoscopically offer reliable low-risk decompression of the biliary tract in patients with unresectable tumors of the pancreas and extra-hepatic biliary tree. In this technique, a diagnostic cholangiogram is obtained via a cannula in the common bile duct. A 300 centimeter-long Teflon® coated guide wire is passed through the cannula beyond the tumor. The catheter is then withdrawn while the guide wire is advanced under fluoroscopic control. A stent is then advanced over the guide wire via a pushing tube. Placement across the stricture is confirmed, after which the guide wire

Table 1. Endoscopic Sphincterotomy — Indications

Retained or recurrent stones post cholecystectomy
Common duct stones in high risk patients with gallbladder <i>in situ</i>
Urgent treatment of acute gallstone pancreatitis
Stenosis of the ampulla of Vater
Preparation for placement of biliary endoprosthesis
Ampullary tumors in poor risk surgical candidates
Dyskinesia of the sphincter of Oddi

Fig 2. An endoprosthesis is in place, bridging a malignant bile-duct tumor.



and pushing tube are removed, leaving the stent in place (Fig 2).

Endoscopic placement of a stent is less traumatic than a percutaneous approach and has the advantage of increased ease of changing equipment if clogging or dislodgement occurs.⁴ Further, failure to place the stent via the percutaneous route may result in an external biliary fistula or bile leak, while failure to place an endoscopic stent generally does not create new problems. Endoscopic stents are a cost-effective alternative to surgical bypass procedures for palliation. In a recent uncontrolled retrospective review of non-operative vs operative biliary bypass in 64 patients with pancreatic carcinoma,¹³ mortality and morbidity were similar, though the non-operative endoscopically-treated groups were older with a decreased preoperative performance status. This study utilized smaller stents than are currently employed, so that subsequent problems with stent clogging and cholangitis or recurrent jaundice would be expected to be more common than with the currently utilized larger endoprostheses. Other uses of endoscopic stents include postoperative strictures, sclerosing cholangitis and biliary fistulae (Table 2). Recent experience has also suggested that very large common duct stones in high-risk patients may be left *in situ* if a stent is passed endoscopically above the stone with the proximal end in the duodenum. In one series of 17 high-risk patients followed for a mean of 39 months, only two of 17 patients (12 per cent) required surgery for biliary sepsis.¹⁴ The stent acts as a wick, and clogging is not a major concern, since the bile can

still drain effectively around the stent. Successful stent replacement has been reported in 80 to 90 per cent of patients in large series.^{4,13} Larger stents (up to 12 French) may require a small sphincterotomy prior to stent placement. Complications of stent placement include those associated with endoscopic sphincterotomy or problems peculiar to endoprostheses. Cholangitis is possible, especially if the stent placement is improper and adequate drainage is not achieved. Most commonly, delayed complications include recurrent jaundice or cholangitis, both of which can generally be managed by endoscopic stent replacement. Rarely, a stent may erode into the wall of the duodenum producing bleeding or duodenal perforation. Periodic replacement of a stent depending on the size of the stent or the nature of the underlying obstruction may obviate some of these potential complications.

Table 2. Biliary Stents — Indications

Palliation of malignant obstruction
Benign biliary stricture
Sclerosing cholangitis
Common-duct stones in high operative-risk patients following failed stone extraction
Biliary fistulas

Balloon Dilatation

Angiographic Gruntzig-type balloons have been adapted to use in the treatment of biliary tract strictures. Indications for manometrically-controlled endoscopic balloon dilatation include management of postoperative strictures, dominant strictures in sclerosing cholangitis, and ampullary stenosis. Small common-bile-duct stones may at times be removed without sphincterotomy by dilating the ampulla of Vater with a balloon and allowing the stones to pass spontaneously or via extraction with a balloon catheter.¹⁰ Balloon dilatation may also be useful in malignant strictures to facilitate passage of large-caliber endoprosthesis.

Future Directions

Equipment refinement and technological advances are widening the clinical utility and spectrum of endoscopic biliary therapy. Current focus of interest is on more effective crushing baskets to fragment large stones, better chemical stone-dissolving agents, electrohydraulic lithotripsy to crush stones with shock waves via an endoscopic cannula, and improved endoscopes.

Limitations of current data include the absence of randomized controlled trials comparing endoscopic management with alternative therapies. A wide range of technical expertise and rapidly changing equipment and technology also make comparison difficult.

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BRIEF SUMMARY

CONTRAINDICATIONS

There are no known contraindications to the use of sucralfate

PRECAUTIONS

Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration

Drug Interactions: Animal studies have shown that simultaneous administration of CARAFATE (sucralfate) with tetracycline, phenytoin, digoxin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. This interaction appears to be nonsystemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The clinical significance of these animal studies is yet to be defined. However, because of the potential of CARAFATE to alter the absorption of some drugs from the gastrointestinal tract, the separate administration of CARAFATE from that of other agents should be considered when alterations in bioavailability are felt to be critical for concomitantly administered drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted

Pregnancy: Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients treated with sucralfate, adverse effects were reported in 121 (4.7%).

Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

OVERDOSAGE

There is no experience in humans with overdosage. Acute oral toxicity studies in animals, however, using doses up to 12 gm/kg body weight, could not find a lethal dose. Risks associated with overdosage should, therefore, be minimal.

DOSAGE AND ADMINISTRATION

The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

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Issued 1/87

Reference:

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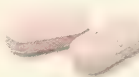
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**ROSALYN P. STERLING-SCOTT, M.D.**

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OUTSTANDING ACHIEVEMENTS Author of numerous articles, including "Indications for Early Bypass Grafting Following Intracoronary Streptokinase"; author of "The Female Surgeon—Dawn of a New Era," chapter in *A Century of Black Surgeons—The U.S.A. Experience*; Board of Directors, Association of Black Cardiologists; Secretary, Drew Society

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PERIPATETICS

The American Society of Echocardiography elected **Dr Alfred F. Parisi**, Chief of Cardiology at Miriam and Roger Williams Hospitals, as its president for 1989-90.

• • •

Assistant Professor of Medicine at Brown and Miriam Hospital, **Dr Peter M. Wiest** has received a five year National Institutes of Health Physician/Scientist Award for the study of schistosomiasis. The research will be conducted with several investigators at Brown.

• • •

Dr James P. Crowley, Associate Director, Division of Clinical Hematology at Rhode Island Hospital and Associate Professor of Medicine at Brown University, was recently certified in Diagnostic Laboratory Immunology by the American Board of Internal Medicine and the American Board of Pediatrics.

• • •

Memorial Hospital of Rhode Island recently appointed **Dr Howard G. Dubin**, Clinical Assistant Professor of Medicine at Brown University, as Director of the Intensive Care Unit.

• • •

The American Federation for Clinical Research has elected **Dr Paul D. Levinson**, endocrinologist at Memorial Hospital of Rhode Island, to a three-year-term as Eastern Section Councilor.

• • •

Memorial Hospital of Rhode Island has announced the appointments of **Dr Andrew R. Hordes** as staff cardiologist to the department of medicine and **Dr Paul Rehkopf** to the staff of the emergency department.

• • •

The American Cancer Society, Rhode Island Division, held its annual meeting in Newport and presented **Dr A. Sattar Memon**, Assistant Clinical Professor of Medicine at Brown University, with the 1988 Public Education Life Saver, Hall of Fame Award for exemplary volunteer services.

Radiologic Case of the Month

(answer on page 113)



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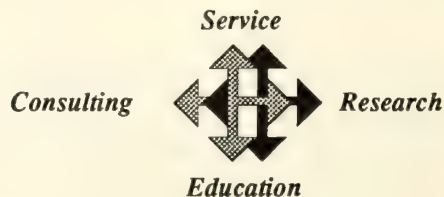
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Recent Abstracts of Interest

Ultrasound May Be Useful in Diagnosing Alternative Conditions in Suspected Acute Appendicitis

Two hundred ninety-seven patients underwent real-time sonography for clinically suspected acute pancreatitis. The study population included the 174 patients in this group who proved not to have acute appendicitis. In this group, 53 per cent were ultimately discharged with a diagnosis of abdominal pain of unknown origin. Of the remaining 81 patients in whom a specific diagnosis was established, sonography suggested the correct diagnosis in 57 patients (70 per cent). Sonographic diagnosis was correct in 21 of the 28 patients with pelvic inflammatory disease, in 12 of the 14 patients with ovarian cysts, and both patients with uterine myomas. In 18 of the 22 patients with visceral abnormalities, including those of hollow viscera and liver, pancreas, or spleen, ultrasound suggested the correct diagnosis. These patients had unsuspected small bowel obstruction diagnosed by detection of dilated fluid filled loops; two cases of diverticulitis were diagnosed on the basis of wall thickening of the cecum, while terminal ileal thickening was present in three patients with infectious enteritis. In addition, detection of peritoneal fluid collections was found in three cases of spontaneous bacterial peritonitis. Ultrasound was also useful in detecting unsuspected urinary tract stones and perirenal hematoma in three and one patient respectively.

Sonography is useful in the differential diagnosis of acute appendicitis only when clinical data is equivocal, thus the group of patients undergoing ultrasound is a skewed selected population. CT scanning has also been utilized in differential diagnostic problems of right lower quadrant pain,

and no comparative study of sonography and CT has been done in this group of patients. This study suggests that in patients with suspected acute appendicitis with atypical symptoms, perhaps only remotely suggestive of appendicitis, that sonography is frequently of value in establishing alternative diagnoses.

Gaensler E.H.L., Jeffrey R.B., Jr., Laing F.C., Townsend R.R. Sonography in patients with suspected acute appendicitis: Value in establishing alternative diagnoses. *American Journal of Roentgenology* 152:49-51, 1989.

Patient History May Be Unreliable in Assessing the Possibility of Pregnancy

Liberal use of tests for pregnancy has been advocated because of the contention that in emergency departments patient history may be an unreliable method of excluding pregnancy. This is a prospective study of 208 patients seen in three University-affiliated emergency departments in whom a qualitative serum beta-HCG determination was performed. The main indication for ordering a pregnancy test was abdominal pain in 138 patients, either alone or associated with gynecologic symptoms, such as vaginal bleeding or discharge. A smaller number of patients presented with specific concern about the possibility of pregnancy or simple syncope or dizziness. Three historical variables were statistically less likely to be associated with pregnancy — last menstrual period that was on time, the patient's subjective impression that she was not pregnant, and the patient's statement that there was no chance she could be pregnant. However, the combination of an on time and normal last menstrual period was associated with a 10 per cent chance of pregnancy, while the combination of

a last menstrual period on time and normal and patient stating that there was no chance she could be pregnant was associated with a 7 per cent chance of being pregnant. In this study, 13.7 per cent of patients using regular birth control had positive beta-HCG tests compared to 38.9 per cent who used no birth control. This study supports the liberal use of pregnancy tests in emergency departments, despite the absence of historical data suggesting pregnancy. This is a study from three large city hospitals in Camden, New Jersey and Philadelphia, Pennsylvania, in which such potential confounding variables, as age, language barrier, socioeconomic group, as well as components involving the physical examination, were not assessed.

Ramoska E.A., Sacchetti M.D., Nepp M. Reliability of patient history in determining the possibility of pregnancy. *Annals of Emergency Medicine* 18:48-50, 1989.

Cancer Patients Commonly Have an Identifiable Cause for Muscle Cramps

Fifty cancer patients with new complaints of localized painful involuntary muscle contractions were prospectively evaluated. The underlying tumors included 40 solid, 7 lymphoreticular, and 3 primary central nervous system tumors. Thirty-two of fifty patients reported onset which was acute (less than 3 months duration). Forty-six percent of patients reported numerous attacks per day equally affecting the upper and lower extremities or both. In 41 patients (82 per cent), a specific neurological, muscular, or biochemical abnormality was identified as the likely cause. Peripheral neuropathy accounted for cramps in 22 patients, and nerve root or plexus pathology was responsible in 17 patients; in 18 per cent no cause was discovered. In 14 patients, cramps were thought to be a complication of malignancy, including leptomeningeal metastasis in 6, epidural root compression in 3, brachial plexus compression in one, and a paraneoplastic syndrome in 4. A complication of therapy was implicated in 21 patients, including chemotherapy induced peripheral neuropathy in 16 and radiation injury in 3. Hypomagnesemia accounted for muscle cramps in only one patient.

In healthy individuals, often no apparent cause can be detected. Symptoms may then be regarded as due to benign muscle cramps. In cancer patients, however, muscle cramps are frequently not a benign complaint and commonly

mark the presence of an identifiable neurologic disorder.

Steiner I., Siegal T., Muscle Cramps in Cancer Patients. *Cancer* 63:574-577, 1989.

An Optimistic Assessment of Surgical Excision of Multiple Liver Metastases

The median survival of untreated patients with hepatic metastasis ranges from three to nine months. Resection of solitary hepatic metastasis has been associated with a five-year survival of 20 to 30 per cent, but multiple hepatic metastases are often ignored surgically. This study reports 98 patients with one or more hepatic metastases who underwent surgical resection; 66 had more than one lesion. Ninety-one of 98 were alive at 12 months, 50 of 71 at 13 to 24 months. Of the 98, 19 were reoperated upon with a rising CEA level as the only indicator, while 66 had a positive CT scan of the liver. Of the 98, 59 had resection of metastasis outside the liver, as well. When four more lesions were removed, hepatic artery and portal vein catheters were placed in the gastropiploic artery and vein for chemotherapy delivery.

This study suggests that an aggressive approach is warranted in some patients with multiple hepatic metastases from colon cancer. However, other studies have reported less favorable results, as well as implicating other factors influencing survival. The factors potentially associated with a more favorable course are well differentiated as opposed to poorly differentiated tumors, earlier stage of the primary tumor independent of the presence of liver metastases, and absence of concurrent extrahepatic metastases. The number of lesions may not accurately reflect the extent of liver involvement. This study does support the importance of adequate tumor-free resection margins.

Minton J.P., Hamilton W.B., Sardi A., Nieroda C., Sicile-Santanello B., O'Dwyer P.J., Results of surgical excision of one to thirteen hepatic metastases in ninety-eight consecutive patients. *Archives of Surgery* 124:46-48, 1989.

Edited by Edward R. Feller, MD

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1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.

3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is a cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics; see **WARNINGS**.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS**, **WARNINGS**, and **OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS**); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 mEq/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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Answer to Radiologic Case of the Month (from page 107)

Calcium pyrophosphate and occasionally calcium oxalate crystals can deposit in menisci and articular cartilage as linear calcifications as seen in the joint space in this patient with chondrocalcinosis. Crystals can deposit in any joint. Knees, wrists, and metacarpophalangeal joints are most commonly involved. Acute attacks of crystal associated arthritis may mimic gout and are termed pseudogout.

Calcium pyrophosphate deposition has been associated with hyperparathyroidism, hemochromatosis, myxedema, ochronosis, hypomagnesemia, and Wilson's disease, as well as being at times present in both osteoarthritis or rheumatoid arthritis. Linear calcifications are readily seen on roentgenograms; aspiration of synovial fluid yields weakly positively birefringent crystals.

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Contraindication: Known allergy to cephalosporins

Warnings: CECLOR SHOULD BE ADMINISTERED CAUTIOUSLY TO PENICILLIN SENSITIVE PATIENTS. PENICILLINS AND CEPHALOSPORINS SHOW PARTIAL CROSS-ALLERGENICITY POSSIBLE REACTIONS INCLUDE ANAPHYLAXIS

Administer cautiously to allergic patients

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics. It must be considered in differential diagnosis of antibiotic-associated diarrhea. Colon flora is altered by broad-spectrum antibiotic treatment, possibly resulting in antibiotic-associated colitis

Precautions:

- Discontinue Cecilor in the event of allergic reactions to it
- Prolonged use may result in overgrowth of nonsusceptible organisms
- Positive direct Coombs' tests have been reported during treatment with cephalosporins
- Cecilor should be administered with caution in the presence of markedly impaired renal function. Although dosage adjustments in

moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made

- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis

● Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Cecilor penetrates mother's milk. Exercise caution in prescribing for these patients

Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include

- Gastrointestinal (mostly diarrhea): 2.5%
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] and toxic epidermal necrolysis or the above skin manifestations accompanied by arthritis/arthritis, and frequently, fever) 1.5%, usually subside within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Cecilor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome

- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely

- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported

- Other: eosinophilia, 2%, genital pruritus or vaginitis, less than 1%, and, rarely, thrombocytopenia

Abnormalities in laboratory results of uncertain etiology

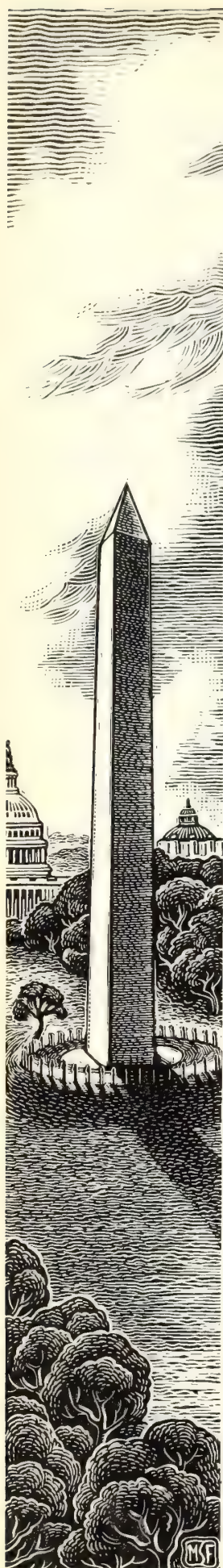
- Slight elevations in hepatic enzymes
- Transient fluctuations in leukocyte count (especially in infants and children)
- Abnormal urinalysis, elevations in BUN or serum creatinine
- Positive direct Coombs' test
- False-positive tests for urinary glucose with Benedict's or Fehling's solution and Clinistix[®] tablets but not with Tes-Tape[®] (glucose enzymatic test strip, Lilly).

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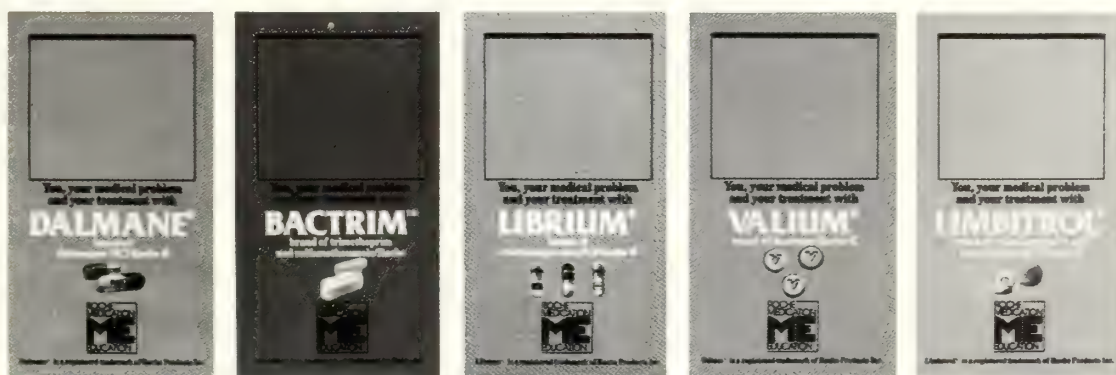


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April 1989

Volume 72, Number 4



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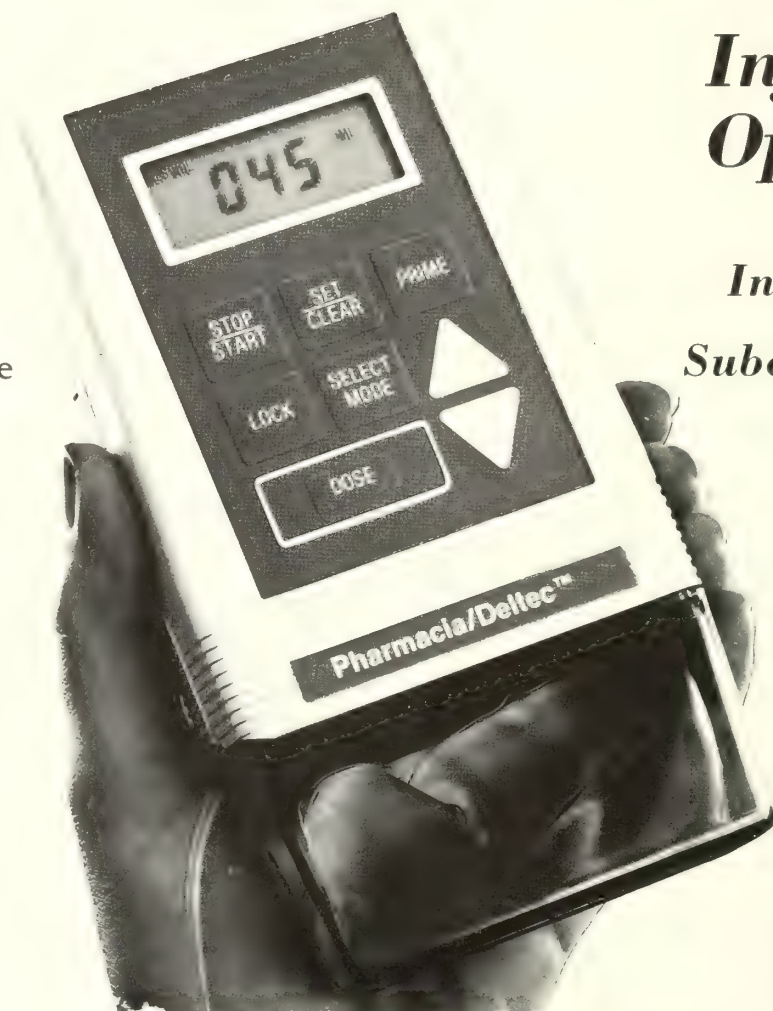


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Cover: *Drawing highlights this month's special issue of the Journal which features papers on complications that may occur during pregnancy.*

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Diabetes and Pregnancy: The Public Health Perspective

In Rhode Island, an estimated 400 females will develop insulin dependent diabetes by age 20, and annually, an estimated 500 women between 15-44 will have gestational diabetes (GDM).^{1,2} As Drs Quevedo and Coustan point out in their article, the incidence of major defects in infants of Type I diabetic mothers is several times that which occurs in infants of non-diabetic mothers. These defects occur prior to the seventh week of pregnancy and are clearly related to maternal glycaemic control. Although malformations are not increased in infants born to women with GDM, there is a higher incidence of perinatal morbidity in these babies.

Reduction of fetal malformations, and perinatal morbidity among babies born to women with diabetes is a major public health challenge, and one that the Centers for Disease Control (CDC) has taken seriously. The potential to reduce perinatal morbidity and mortality by early intervention for Type I diabetic women planning to become pregnant, and by early identification of women with GDM, cannot be overstated. Additionally since 40-60 per cent of women with GDM will eventually develop Type II diabetes,³ identification and close post-partum and long-term follow-up of these women presents a golden opportunity to decrease the neurologic, cardiovascular, renal and ophthalmologic complications of uncontrolled Type II diabetes.

In order to address their concerns regarding diabetes and pregnancy, the CDC has five goals for public health agencies:⁴

1. To ensure screening of all pregnant women for GDM.
2. To ensure preconception identification of all diabetic women who may become pregnant.
3. To ensure appropriate care for pregnant diabetic women.
4. To ensure comprehensive post-partum care and care for subsequent pregnancies.
5. To ensure comprehensive post-partum and long-term care for women with GDM to prevent long-term complications should type II diabetes develop.

To address the goals of the CDC, the Rhode Island Health Department has begun discussion to develop a Diabetes and Pregnancy Advisory Council in order to promote professional and public awareness of the importance of good glycaemic control prior to and throughout pregnancy, and the importance of screening for GDM. The suggestion of Drs Quevedo and Coustan to create a voluntary registry of diabetic women of child-bearing age is excellent and the Health Department can contribute to that effort.

Since low-income pregnant women with diabetes are at even greater risk, two Health Department programs targeting low-income pregnant women are particularly important resources for this group. The RIte Start program was developed to improve pregnancy outcome by providing comprehensive prenatal and perinatal care to uninsured pregnant women at numerous sites throughout the State. The Women Infants Children (WIC) program provides low-income pregnant women and new or breastfeeding mothers with nutrition education and financial assistance to purchase nutritious foods for themselves and their children aged five years or younger.

The pregnant diabetic woman presents a major challenge for both the public and private health care sectors. Our success at meeting this challenge will insure the health and well-being of thousands of individuals in Rhode Island in the years to come.

Judith Feldman, MD, MPH
Chief, Chronic Disease
Rhode Island Department of Health

For information on the RIte Start program, call 277-2312 or 1-800-346-1004. Call 277-3940 or 1-800-WIC-RIDH for information on the Women Infants Children program.

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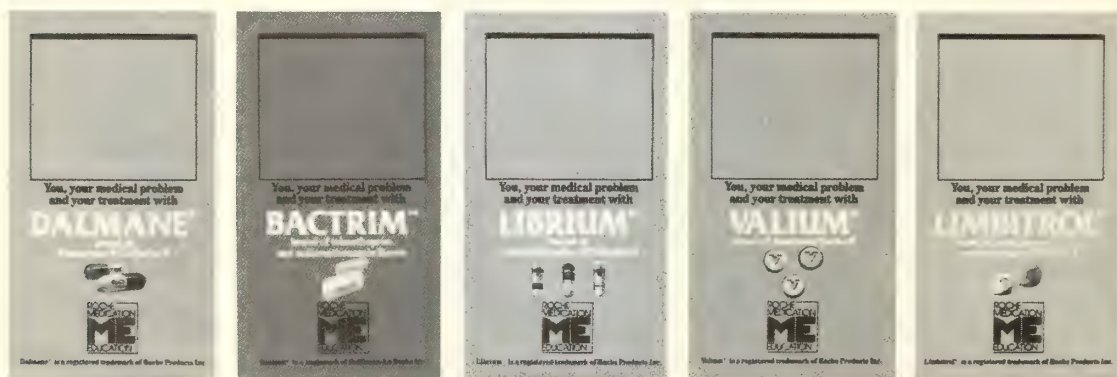


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Acute Renal Failure in Pregnancy

Management Depends Upon Cause, But Dialysis May Be Necessary

Douglas Shemin, MD
Joseph A. Chazan, MD, FACP

Acute renal failure occurs rarely during pregnancy in the United States; recent reviews of the topic cite an incidence of between 1:5000 to 1:20,000.¹⁻³ Earlier reviews, published in the 1950s and 1960s, report a higher incidence, of approximately 1:1500.⁴ Moreover, these studies note that episodes in pregnancy account for up to 15 per cent of all cases of acute renal failure reported.⁴ Studies from India⁵ and Algeria³ still report a high incidence of renal failure associated with obstetrical problems. Most of these cases represent episodes of acute tubular necrosis oc-

curing as a complication or consequence of septic abortions. The liberalization of abortion laws in the United States contributes to the decrease in the incidence of acute renal failure in pregnant women in this country.²

Nevertheless, acute renal failure still occurs in pregnancy and in the postpartum period. This paper will discuss briefly the principal causes, including 1) the HELLP syndrome, 2) acute fatty liver of pregnancy, and 3) postpartum renal failure, that occur exclusively during or after pregnancy.

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Renal Physiologic Changes

Clinically relevant renal physiologic changes occur during normal pregnancy. Most importantly, effective renal plasma flow and glomerular filtration rate increase to levels 50-70 per cent above the non-pregnant state. These developments occur in conjunction with an increase in total body water by 6 to 8 liters and a gradual retention of up to 900 mmol of sodium.⁶ For reasons that are not well understood maternal volume and osmotic receptors perceive these changes to be normal; thus, aldosterone and antidiuretic hormone continue to be released, maintaining a state of chronically elevated extracellular fluid volume.

It is important to note that this volume expansion results in a fall in serum creatinine levels to a new "normal" value of between 0.2 and 0.7 mg/dl. Any value higher than this probably reflects

some degree of renal functional impairment. The failure of clinicians to recognize this may explain some under-recognition and under-reporting of mild cases of renal failure during pregnancy. It is important to keep this in mind especially in patients with associated hypertension, or proteinuria, or both.

Prerenal and Postrenal Failure

The evaluation of pregnant women with acute renal failure should be similar to the evaluation of renal failure in any other setting. Two broad categories of etiologic causes not affecting the renal parenchyma need to be considered. First, prerenal failure is associated with a decreased effective intravascular volume, decreased renal blood flow, and decreased oxygen delivery. Second, postrenal failure, due to urinary tract obstruction from the renal collecting system to the urethral orifice, results in increased pressure causing complete or partial obstruction to urine flow.

A marked diminution of extracellular volume, usually secondary to extensive gastrointestinal losses or occasionally due to insensible fluid losses, anorexia, decreased oral intake, or hemorrhage is typically responsible for prerenal failure. Pregnant women are protected against developing a large volume deficit because their extracellular volume is already significantly increased as a result of the physiologic changes detailed above. Hyperemesis gravidarum, or severe vomiting in the first trimester, is rarely associated with renal failure.⁷

Bleeding, especially from the uterus in the case of placenta previa, abruptio placentae, or postpartum hemorrhage, is probably responsible for most cases of prerenal failure in pregnancy. Replacement of volume losses, along with control of bleeding, should restore renal function to normal in most cases.

Pregnant women have an increased risk for urinary tract obstruction and postrenal failure because of two unique physiologic developments. First, as the gravid uterus enlarges, it may compress the ureters which lie posteriorly and may thus cause ureteral obstruction. This risk would appear to be enhanced with polyhydramnios, multiple gestations, or retroflexion of the uterus. However, renal failure as a result of these causes appears to be very rare.⁷⁻¹⁰ Second, under the influence of progesterone, ureteral and renal pelvic tone relaxes during pregnancy, causing a mild hydronephrosis and hydroureter. This appears to be a purely radiologic phenomenon, and is not associated with clinical renal failure.⁶

Intrinsic Renal Failure

Renal failure due to parenchymal changes within the kidney results from a variety of disorders which can occur in both the pregnant and non-pregnant state. Tubulointerstitial disease, such as acute tubular necrosis or interstitial nephritis, and renovascular disease, such as that due to atheroembolism, are relatively rare in pregnancy. Their development is commonly exacerbated by a host of co-morbid conditions such as sepsis, hypotension, hypoxia, peripheral vascular disease, heart failure, or hepatic cirrhosis, disorders which are not commonly found in an otherwise normal pregnancy. These causes of renal failure are frequently a consequence of exposure to nephrotoxins such as aminoglycosides, antifungal antibiotics, nonsteroidal anti-inflammatory drugs, and radiocontrast dye, which are infrequently prescribed during pregnancy. Finally, volume depletion is usually a contributory factor in the development of renal failure, and pregnant women are relatively protected against this condition because of the initial elevation in extracellular volume.

Historically, acute tubular necrosis has been the most common cause of renal failure associated with pregnancy, but usually follows abortion, either as a consequence of infection, disseminated intravascular coagulation, or the use of nephrotoxic abortifacients.⁵ Nevertheless, acute tubular necrosis can occur even in the absence of marked sepsis or hypotension; we recently cared for a patient who developed acute renal failure requiring dialysis in the second trimester in conjunction with a relatively mild non-A, non-B hepatitis.¹¹

Glomerular causes of acute renal failure are also rare. Acute glomerulonephritis, with hypertension, proteinuria, and hematuria, may follow a streptococcal infection or occur without obvious cause. It may be difficult to differentiate this process from pre-eclampsia, but the latter generally represents during the third trimester, is not associated with red blood cells casts in the urinary sediment, is uncommonly associated with azotemia, and resolves after delivery.¹

Patients with chronic glomerular diseases, such as diabetic nephropathy, lupus nephritis, focal sclerosis, and IgA nephropathy, may rarely become pregnant. In a study of twelve pregnant women with chronic glomerular disease, about half had a major and accelerated decline in their renal function in conjunction with their pregnancies.¹²

Causes of Renal Failure Unique to Pregnancy

There are three causes of renal failure which occur exclusively in pregnant women:

1) The HELLP syndrome is characterized by hemolysis, elevated liver enzymes, and a low platelet count with variable renal manifestations. In one series of 57 patients, hypertension and proteinuria were present in virtually all patients, but azotemia was a feature in only about half the cases.¹³ The syndrome is very rare, but is exclusively associated with and probably represents a complication of untreated pre-eclampsia.

2) Acute fatty liver of pregnancy is also extremely rare, with an estimated incidence of 1:13,000 pregnancies.¹⁴ It occurs in the third trimester, and clinical manifestations include nausea, vomiting, epigastric pain, and abnormal liver function tests. It differs from viral hepatitis in that transaminase levels are usually less than 500 IU/L, and renal failure is a universal finding. The diagnosis can be made by demonstration of a high hepatic fat content by ultrasound, computed tomography (CT) scan, or a liver biopsy showing steatosis of the centrilobular hepatocytes. Although the etiology is unknown, associations with viral syndromes, tetracycline therapy, and pre-eclampsia have been suggested.¹⁴ The treatment of choice is emergency delivery, which is usually associated with prompt resolution of both the renal and hepatic abnormalities.

3) Postpartum renal failure is similar to hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP); it is characterized by renal failure, thrombocytopenia, and microangiopathic hemolytic anemia. It occurs anytime from hours to weeks after an otherwise normal pregnancy; it is very rare, and less than 100 cases have been reported.¹⁵ The etiology is unknown, although viral illnesses and the use of postpartum oral contraceptive agents has preceded some cases. As in HUS and TTP, renal failure results from deposition of platelet thrombi in the microvasculature of the kidney, leading to ischemia and infarction. It is not clear whether platelet thrombosis is a primary consequence of a deficiency of prostacyclin, an inhibitor of platelet aggregation, or whether it follows a sepsis-induced endothelial cell injury.

Historically, postpartum renal failure has been associated with high morbidity, including a high incidence of irreversible renal failure, and a high mortality. The therapies of plasma infusion or plasma exchange, which replenish prostacyclin, along with antiplatelet agents, have been advocated as treatments of choice to prevent platelet

thrombosis. If treatment is administered early enough to prevent irreversible infarction of the renal microcirculation, renal failure could theoretically be reversed.¹⁵

Management

In conclusion, acute renal failure is a rare complication of pregnancy, with a large number of possible etiologies, some exclusively associated with pregnancy. The specific management depends upon the cause; but, as in any patient with renal failure, dialysis may be necessary in the event of volume overload, hyperkalemia, acidosis, or uremic symptoms.

Exact guidelines for dialysis in pregnancy have not been established, and a discussion of them is beyond the scope of this paper. It has been suggested that blood urea nitrogen levels below 60 mg/dl are associated with increased fetal viability, but the data to support this notion is limited.¹¹ Although hemodialysis has generally been utilized, peritoneal dialysis has also proved to be both safe and effective.¹⁶

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Carcinogenesis, Mutagenesis, Impairment of Fertility: — A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplasia and increased liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a two-generation, prenatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy — Teratogenic Effects — Pregnancy Category C: — Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belled rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect, but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spinal hydrocephalus, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: — Studies conducted in lactating women have shown that <0.1% of the administered oral dose of nizatidine is secreted in human milk in proportion to plasma concentrations. Caution should be exercised when administering nizatidine to a nursing mother.

Pediatric Use: — Safety and effectiveness in children have not been established.

Use in Elderly Patients: — Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo. Among reported adverse events in the domestic placebo-controlled trials, headache (1.1% vs 0.2%), urticaria (0.5% vs < 0.01%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A variety of less common events was also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic: — Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients and was possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L) and, in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular: — In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

CNS: — Rare cases of reversible mental confusion have been reported.

Endocrine: — Clinical pharmacology studies and controlled clinical trials showed no evidence of antihandrogenic activity due to Axid. Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic: — Fetal thrombocytopenia was reported in a patient who was treated with Axid and another H₂-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumentary: — Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity: — As with other H₂-receptor antagonists, rare cases of anaphylaxis following administration of nizatidine have been reported. Because cross-sensitivity in this class of compounds has been observed, H₂-receptor antagonists should not be administered to individuals with a history of previous hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other: — Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine administration have been reported.

Overdosage: Overdoses of Axid have been reported rarely. The following is provided to serve as a guide should such an overdose be encountered.

Signs and Symptoms: — There is little clinical experience with overdosage of Axid in humans. Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous median lethal doses in the rat and mouse were 301 mg/kg and 232 mg/kg, respectively.

Treatment: — To obtain up-to-date information about the treatment of overdose, a good resource is your certified regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the Physicians' Desk Reference (PDR). In managing overdose, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance.

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Diabetes and Pregnancy

Use of an Integrated "Team" Approach Provides the Necessary Comprehensive Care

Stephen F. Quevedo, MD
Donald R. Coustan, MD

Pregnancy complicated by diabetes, whether preexistent or acquired gestationally, can cause anxiety for patient and physician. Historically, this concern is well-founded, as major perinatal morbidity and mortality were associated with this combination before the age of modern obstetric care. Recent advances in our understanding of the etiologies of these complications leading to changes in medical and obstetric care have improved outcomes dramatically.

Type I Diabetes And Pregnancy

Before the availability of insulin therapy, a diagnosis of Type I diabetes was rarely compatible with a successful pregnancy outcome. The beneficial effects of good control of glucose levels

have been known for a half-century with Skipper reporting in 1933:

"to prevent the intra-uterine death of the foetus or its excessive development, the level of the blood sugar must be carefully watched throughout pregnancy, especially during the latter months."¹

Since then, studies have shown a linear relationship between third trimester mean maternal blood glucose and perinatal mortality (figure 1) with specialized centers currently reporting incidences approaching those of nondiabetic pregnancies.² In order to accomplish such results, sophisticated multiple-injection insulin regimens are employed to ensure diabetic control approaching normalcy, with patients performing self glucose monitoring four to six times daily. Because the target glucose values in pregnancy are within the normal, nondiabetic range (less than 90-140 mg/dl), at which levels urine testing is useless and visual interpretation of glucose oxidase strips can be inaccurate, glucose reflectance meters are a requirement. Care of these patients is best achieved by coordinated "teams" of health-care specialists, experienced in the management of diabetic pregnancy. These teams are variously constituted, and may include a combination of

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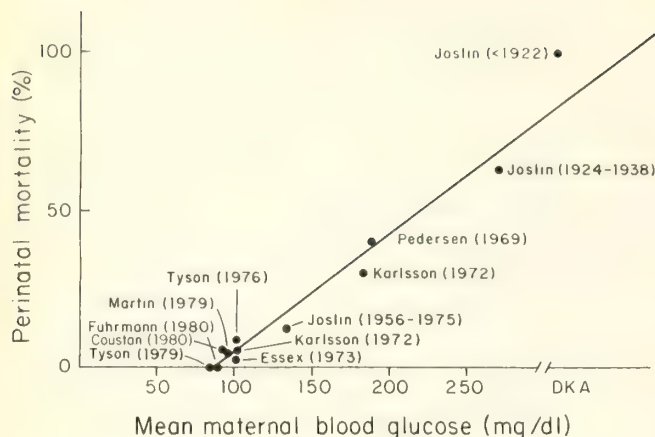


Fig. 1. Relationship between third trimester glucose control and perinatal mortality rates in published series. Adapted from Jovanovic and Peterson [2]. Printed with permission of the American Diabetes Association, Inc. and Dr Jovanovic.

internists, obstetricians, diabetologists, maternal-fetal medicine specialists, and pediatricians, working closely with nurses, nurse-clinicians, diabetes educators, nutritionists, social workers and other health professionals.²⁻⁴ Perinatal morbidities, such as macrosomia, hypoglycemia, birth trauma, and hypocalcemia are also reduced with such care.

The impact of modern obstetric care on the diabetic pregnancy cannot be overstated, and nowhere is this more apparent than in the timing of delivery. Assessment of fetal well-being in the late third trimester with regular antepartum testing, and evaluation of lung maturity with amniocentesis, help to determine the appropriate gestational age for delivery, thus minimizing the risks of respiratory distress syndrome.⁵

Today's Challenge: Congenital Malformations

Despite these advances, an increased incidence of major congenital malformations in the infants of Type I diabetic mothers remains a serious public health problem. Although anecdotal mention of malformations appeared as early as the 1930s, systematic reports of an increased incidence of birth defects appeared in the mid-1960s and early 1970s.⁶⁻⁷ Studies since have revealed rates of major defects (usually involving the heart, great vessels or nervous system) in the infants of Type I diabetic mothers ranging from 5 to 11 per cent, several times that of the general population.⁷⁻¹² The psychological, social and financial costs to family and society are great: therefore public health policy has begun to focus on prevention.

Modern research has made two important discoveries: these malformations occur before the seventh gestational week, and their incidence is clearly related to maternal glycemia during this crucial period of organogenesis.⁸⁻¹² The implications for prevention are obvious. Many women are not even sure of pregnancy until the third to fifth week. Therefore, any attempts to reduce this excess of malformations must try to insure that the mother is in optimal diabetic control from the time of fertilization through the seventh week of pregnancy. Pre-pregnancy counselling and education, and close follow-up around the time of conception to insure good glycemic control, are required in order to reduce the incidence of malformations.

Given the obvious potential public health benefits, several states and Canadian provinces have already begun programs to address this problem.¹³⁻¹⁴ The most logical approach would seemingly be to target a population of diabetic women of childbearing age, create a voluntary registry of those who may desire future pregnancy, and to involve them in an ongoing educational and support program.

Recently, yet another potential benefit of good first-trimester control was discovered; a finding that severe hyperglycemia in this period correlates with an increased risk of spontaneous abortion.¹⁵

Gestational Diabetes

Gestational diabetes, that which is diagnosed first during pregnancy without a previous history of maternal diabetes, has a prevalence of approximately three to four per cent. This is about ten times the prevalence of Type I diabetes, and therefore represents a significant public health concern. It usually presents in the late second trimester when demands on the maternal pancreas are peaking, and its presence is associated with factors known to be associated with decreased pancreatic reserve: maternal age and obesity, family history of Type II diabetes, previous history of a large child or of gestational diabetes, and a history of recurrent spontaneous abortion or stillbirth.

The criteria for diagnosis of gestational diabetes using the oral glucose tolerance test were first developed by O'Sullivan in 1964, and present standards are derived from his work.¹⁶ The most commonly used values are those proposed by the National Diabetes Data Group in 1979, which correct for the use of plasma or serum rather than whole blood. At Women and Infants

Hospital of Rhode Island, the currently used diagnostic thresholds are somewhat different, since they also correct for changes in modern glucose testing methodology.¹⁷ Both sets of criteria are listed in Table 1. Interestingly, despite their great utility in monitoring diabetic control, glucose reflectance meters have not been found precise enough for screening or diagnosis of gestational diabetes.¹⁸

Table 1 — Glucose Tolerance Test Criteria

	(Plasma Glucose in mg/dl)			
	Fasting	1 Hour	2 Hours	3 Hours
National Diabetes Data Group	105	190	165	145
Women & Infants	95	180	155	140

Testing is done with a 100 gram glucose challenge after an overnight fast and 2-3 days of unrestricted carbohydrate diet. Testing utilizes plasma and glucose oxidase or hexokinase methodology. If any two or more values are met or exceeded, gestational diabetes is diagnosed.

Before the age of modern obstetric care, perinatal mortality was increased in gestational diabetes.¹⁹ Largely because of prompt diagnosis and more intensive follow-up care, with improved glucose control and early identification of babies "in trouble," perinatal mortality in gestational diabetic pregnancies now is similar to that in the general population. As malformations are also not increased, attention has focused on the increased perinatal morbidity of the infants of gestational diabetic mothers, including macrosomia (large infants), birth trauma, neonatal hypoglycemia and hypocalcemia. Much research during the 1970s to mid-1980s focused on therapeutic trials of diet alone versus diet and insulin therapy, largely because of a growing conviction that fetal hyperinsulinemia, secondary to maternal hyperglycemia, was responsible for much of the increased morbidity. In most studies insulin therapy, even when given in relatively fixed dosage schedules, reduced the rate of perinatal complications.²⁰⁻²¹

During the 1980s, the detection and care of gestational diabetes has further improved. Standard screening until recently targeted only women over thirty and those with risk factors, although critical evaluation of this approach suggests that fully one-third of cases would be missed.²² However, in 1980 the International Workshop-Conference on Gestational Diabetes Mellitus recommended a glucose challenge screening test at 24-28 weeks gestation for all

pregnant women. In 1985, the Second International Workshop-Conference on Gestational Diabetes reinforced that suggestion.²³ This group specified a 50 gram, 1-hour challenge test, with a plasma glucose level of 140 mg/dl or more being the threshold for performing a full 100 gram, 3-hour glucose tolerance test. At Women and Infants Hospital of Rhode Island a threshold of 130 mg/dl is used, as 10 per cent of gestational diabetics may have screening test values between 130 and 139 mg/dl.²²

One of the benefits of this approach has been an appreciation that gestational diabetes is not a strictly homogeneous disorder, but involves a range of glucose metabolic abnormalities. A revised patient classification has appeared which distinguishes Class A patients, who never develop fasting hyperglycemia, from Class A/B patients, who manifest elevated fasting glucose values.²⁴ While this classification is helpful in distinguishing different mechanisms of maternal metabolic derangement, it is also true that patients with post-prandial glucose elevations but normal fasting levels should be treated aggressively. Patients have gestational diabetes for only a limited time, and prompt treatment of hyperglycemia, with insulin if necessary, is required in order to optimize perinatal outcomes.

The use of self glucose monitoring can greatly improve the care of gestational diabetes, with the most obvious advantage being improved outpatient efficacy of insulin regimens. Other benefits may also be seen, including an enhanced effectiveness of diet, as the patient gets almost immediate feedback about her nutritional choices, and earlier and more thorough detection of diet failure or hyperglycemia, allowing institution of insulin therapy without delay.²⁵ In other words, in those patients able to use it, self glucose monitoring targets the patients who will most benefit from insulin therapy, while prophylactic insulin therapy of all would treat needlessly a large percentage. Another area of active current research involves the significance of even minor degrees of glucose intolerance in pregnancy. Some studies suggest increased perinatal morbidity in patients with screening glucose values considered to be borderline or even within the upper limit of the currently accepted normal range, although the clinical relevance of these findings remains uncertain.²⁶⁻²⁷

As in the care of Type I diabetes in pregnancy, use of an integrated "team" approach provides the necessary comprehensive care, whether in an office, hospital or HMO setting.²⁸ Although all

but a few per cent of these patients will return to normal glucose tolerance almost immediately upon delivery, postpartum counselling remains important. These patients are at a clearly increased risk for recurrent gestational diabetes in subsequent pregnancies, and just as importantly a history of gestational diabetes is associated with a greater incidence of Type II diabetes in later life. During a twenty year follow-up, as many as 40-60 per cent have developed Type II diabetes.²⁹ This eventuality is clearly increased by obesity, and education to help the new mother realize the importance of achieving and maintaining ideal body weight after delivery is worthwhile.

More detailed information on diabetes mellitus in pregnancy is available for those wishing to pursue it.³⁰

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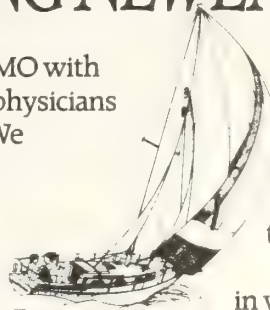
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Coagulopathy and Bleeding in the Parturient Patient

Recent Information Has Helped in the Identification of Individuals at Special Risk

James P. Crowley, MD

Almost from the moment of conception, a series of changes occur in the body of a pregnant woman that tend to make her blood clot more easily. These changes are beneficial since they favor the preservation of the fetus should bleeding occur. As the pregnancy advances, particularly at the time of delivery, there is a corresponding increase in the ability of the patient to lyse clots. This is important in maintaining the patency of the placental circulation in the face of an increase in local clot formation as the placenta matures. In the vast majority of pregnancies, the opposing forces of hypercoagulability and enhanced fibrinolysis remain well balanced although tilting to the former. Neither overt thrombosis nor bleeding occur. However, in a variety of situations to be discussed, in some women the balance is lost. The enhanced tendency to clotting and lysis results not only in thrombosis, but also in the consumption of platelets, clotting proteins or both which results in a serious hemorrhagic tendency. It has been six years since this subject has been comprehensively reviewed here with respect to

the high risk mother and fetus.¹ It is worthwhile to do so now since in the interim, much has been learned to clarify how the homeostatic balance between clotting and lysis may be upset. Moreover, many of these new observations have important clinical implications.

I. Normal Hemostasis

When a blood vessel is disrupted, reflex vasoconstriction occurs that slows blood flow and platelets aggregate to form a gelatinous plug. Their normally discoid shape changes to that of a spiny sphere which causes them to mesh with one another. Mechanical stimulation of the platelet surface results in the release of arachidonic acid which activates the cyclooxygenase pathway. This in turn gives rise to thromboxane A₂ (TxA₂) which is a potent amplifier of the local hemostatic response by its markedly stimulatory effect on platelet aggregation on vasoconstriction. Aspirin produces its effect by inhibiting this step in hemostasis. Almost simultaneous to the formation of TxA₂, platelets begin to release adenosine diphosphate which both tightly aggregates the tangled platelet plug and recruits other platelets. The entrapped platelets release vasoactive amines and rearrange their abundant phospholipids to expose an activity termed platelet factor 3 (PF3) that can directly activate factor X which is very efficient in catalyzing the conversion of prothrombin to thrombin.² The importance of the platelet phospholipid surface on the rate of prothrombin conversion is evident by the observation that on the platelet surface, bound factor Xa can produce the same amount of thrombin in

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two minutes as would be generated in one year by free Xa! In addition to these important platelet mediated events, when blood vessels are damaged, Factor VII and Factor XII are converted into active forms that activate specific proteolytic enzymes which form the extrinsic and intrinsic pathways of coagulation.

The conversion of prothrombin to thrombin is the key to definitive clot formation. Visible clot formation begins with the conversion of fibrinogen to monomeric fibrin which rapidly polymerizes. Factor XIII completes this process by covalently linking the polymerized fibrin which greatly enhances its tensile strength.³ Thrombin has been called the "master enzyme of coagulation."⁴ It cleaves not only fibrinogen but also FXIII, V, VIII, and prothrombin. In minute amounts it aggregates platelets, and also causes smooth muscle contraction thus potentiating the primary response of the blood vessel to injury.⁵⁻⁷ Thrombin converts fibrinogen to a fibrin monomer by cleaving four small peptides designated A and B from the amino terminal end of its two principal, alpha and beta polypeptide chains. The release of these fibrinopeptides exposes highly reactive positively charged regions that have high affinity for the terminal or D domain of the fibrin molecule which initiates the formation of a highly polymerized fibrin clot. Factor XIII covalently crosslinks these long fibrin polymers to form a tough, resilient mass that completes the clotting process and prevents further bleeding.

II. Normal Inhibition and Lysis of Clots

The clotting mechanism if unchecked has the potential to cause a complete gelation of the blood with a consequent cessation of blood flow and oxygen delivery. Accordingly, there have evolved potent mechanisms to inhibit clot formation, and limit the spread of clotting beyond the areas in which it is useful. The principal substances involved in this inhibition and inactivation are antithrombin III (ATIII) and Protein C (PC). The former is a circulating polypeptide that inhibits circulating prothrombin as well as activated factors XII, XI, X, IX. The rapidity with which it promotes inactivation is greatly enhanced by even small amounts of heparin. It is a hallmark of patients deficient in this substance that they are difficult to anticoagulate with heparin. ATIII binds covalently to thrombin and other susceptible activated factors and is cleared as a complex by the liver. Thus in states of marked thrombin activation depletion of ATIII is sometimes observed. Protein C is a vitamin K dependent pro-

tein that is released from an endothelial receptor, thrombomodulin. Secreted PC is activated by thrombin to a potent anticoagulant activity that selectively cleaves activated FV and VII thus decreasing the new formation of thrombin. The inactivation of Factor Va by PC on the surface of platelets is greatly potentiated by another vitamin K dependent factor, Protein S. Patients with congenital absence of PC or its cofactor Protein S suffer from massive thrombosis in the form of neonatal purpura fulminans.^{8,9}

As thrombin is inactivated, clot formation will cease and the process of clot dissolution and repair of the damaged blood vessels begins. The first step is in the lysis of fibrin in the clot which is mediated by a class of enzymes called plasminogens. Plasminogen is an enzyme that circulates in the blood. Two forms of activators of plasminogen exist, proenzymes in the circulation and latent, tissue plasminogen activators (TPA) that exist in a bound form within cells. The principal circulating activator is the Hageman factor, Factor XII, which also initiates clotting. Extrinsic TPA is more important physiologically in limiting thrombosis. Recently recombinant TPA has been available and is an effective agent for the rapid lysis of recently formed clots such as occur in acute myocardial infarction. Once activated, plasminogen is capable of rapidly digesting fibrin,¹⁰ but it also has the same effect on fibrinogen and factors V and VIII so it is not surprising that uncontrolled fibrinolysis rapidly results in the depletion of all these major factors and a severe bleeding tendency may occur.

The principal inactivator of plasmin is termed alpha 2 antiplasmin which binds to plasmin in a reaction that is among the most rapid of all protein-protein interactions.¹⁰ Plasminogen degraded fibrinogen breaks up into five major fragments of which the last two, D and E are the most important quantitatively. Systemic release of the D fragment can damage endothelial cells and if the normal clearance of D fragments by the reticuloendothelial system (RES) is overwhelmed, then platelet clumping and increased vascular permeability, particularly in the lungs, can result.¹¹

III. Changes in the Coagulation System During Pregnancy

An increase in virtually all clotting factors occurs during pregnancy.¹²⁻¹⁵ An important exception is Protein S, the co-factor of the natural anticoagulant Protein C which falls significantly.¹⁶ Activated clotting factors including Xa^{17,18} are found in the circulation of many patients. Increased

levels of fibrin degradation products were found in 60 per cent of pregnant women in one study.¹⁹ Evidence that these increases are actually associated with *in vivo* fibrin formation is found in a smaller fraction of patients in whom fibrin monomers or fibrinopeptide A also circulate.²⁰ Antithrombin III levels have been found to be decreased in some studies,²¹ but not invariably.^{14, 22} Depressed levels of plasminogen activators occur during pregnancy in both the plasma and in venous walls.²³ Inhibitors of plasminogen activation have been demonstrated in the placenta.²⁴ It has been supposed but not proven that local consumption of clotting factors in the uteroplacental circulation may be responsible for these changes. In the absence of definitive studies, it seems reasonable to postulate that inhibition of plasminogen activation in the placenta may create a favourable environment for clot formation locally which leads to fibrinogen consumption and clotting factor activation, and that in the setting of increased steroid hormones,²⁵ this process may become generalized if a further stimulus to clotting occurs. It is important to screen all patients who have a history of repeated thrombosis and thrombophlebitis for hereditary or acquired deficiencies in Protein C or Protein S since these are associated with a striking increase in thrombotic problems during pregnancy.²⁶⁻²⁹

Table 1 — Risk Factors for Thrombosis in Pregnancy

- 1 Prior history of thromboembolic disease
- 2 Lupus anticoagulant
- 3 Low antithrombin III, Protein C or S levels
- 4 Prolonged immobilization
- 5 Massive varicosities
- 6 Obesity
- 7 Inflammatory bowel disease
- 8 Nephrotic syndrome
- 9 Estrogen therapy
- 10 Infection

IV. Coagulation Problems Primarily Related to Platelet Activation

The role of the platelet activation in providing an additional stimulus to clotting in many patients is emphasized by the recent finding of elevated TxA₂ levels in late pregnancy.³⁰ Whether there is a normal fall in platelet count during late pregnancy³¹ is controversial. Studies that have carefully excluded women with preeclampsia or placental lesions have not found any difference between the platelet count of normal and pregnant women.^{32, 33} A recent study by Burrows and Kelton³⁴ showed that 8.3 per cent of pregnant

women exhibited platelet counts between 97-150,000 which were not associated with either bleeding or thrombosis nor was there fetal or maternal morbidity. The nature of this mild thrombocytopenia was unclear, but it was to be distinguished from patients with platelet counts below 100,000/ul since most of these will be due to immune thrombocytopenia purpura or some other condition requiring therapy. Conditions in which thrombocytopenia may be the sole evidence of coagulopathy are described in this section.

1. Preeclampsia/Eclampsia

Preeclampsia and its more severe form, eclampsia, is the most common cause of maternal death. Preeclampsia/eclampsia (P/E) is accompanied by elevated peripheral resistance, increased mean arterial blood pressure (MAP) and increased permeability of the vasculature. Salt retention is a familiar feature as is edema.^{35, 36} Pritchard et al.³⁷ observed thrombocytopenia in 29 per cent of cases and hemolysis in two per cent and other reports documented that even with massive hemolysis consumption of clotting components was minimal or absent altogether.³⁸ Remuzzi and colleagues reported a reduced concentration of prostacyclin in both the umbilical artery and placental veins of patients with P/E and postulated that the reduced concentration of prostacyclin elevated vascular resistance and impaired the perfusion of the placenta thus reducing oxygen delivery to the fetus.³⁹

Hypoalbuminemia reduces the inhibitory effects of prostacyclin on platelet aggregation⁴⁰ and further aggravates the tendency to platelet activation. The secondary effects of hemoconcentration will also augment this process by increasing the potential for platelet-vessel wall interaction by increasing the concentration of platelets that are close to the vessel wall. Even in a normal pregnancy, the viscosity of blood is increased secondary to the increase in fibrinogen that enhances rouleaux formation.⁴¹ And this tendency is even more enhanced in patients with P/E. The fundamental basis for P/E is still unknown. The primary lesion is likely to reside in the endothelial cell. Efforts to study this cell in pregnancy have been greatly hampered by the relative inaccessibility of endothelial cells and the uncertainties that surround normal endothelial function in health and disease.

Therapy is supportive for the most part. Heparin has been shown to be ineffective.⁴² Hemodilution will reduce the MAP and increase serum estriol levels signalling improved fetoplacental

perfusion.⁴³ Based on the studies of Remuzzi et al.,³⁹ it seems rational to employ prostacyclin. Preliminary studies have indicated a favorable response of the MAP to this treatment⁴⁴ but it is not known if this approach will improve either maternal or fetal mortality. Plasma exchange has been beneficial in the control of thrombotic thrombocytopenic purpura (cf. below), another disorder in which there is reduced prostacyclin concentrations, and deserves consideration in severe cases of P/E refractory to conventional management. A few clinicians have given aspirin to P/E patients and observed a rise in platelet count but there are no controlled studies to indicate its usefulness. In the absence of data, the risks of ASA seem small if the blood pressure is controlled.

Table 2 — Disorders Primarily Related to Platelet and Endothelial Abnormalities

- 1 Preeclampsia/eclampsia
 - 2 Hemolytic uremic syndrome (HUS)
 - 3 Idiopathic thrombocytopenic purpura (ITP)
 - 4 Thrombotic thrombocytopenic purpura (TTP)
-

2. Immune Thrombocytopenia Purpura

ITP is not strictly a coagulopathy but is mentioned here because it is often prominent in the differential diagnosis of preeclampsia/eclampsia. ITP is an autoimmune process in which an antibody, usually of the IgG type, is directed to platelet antigens with a resultant destruction of the platelets in the spleen. It is most common in young women and for this reason occasionally complicates pregnancy. Although their normal concentration is between 200-400,000/ul, as little as 7,000/ul will maintain normal vascular integrity and even with active trauma there appears to be little additional bleeding when platelet levels are as low as 50,000/ul.⁴⁵ Maternal complications of ITP are generally low but exacerbations during pregnancy are common.⁴⁶ IgG may cross the placenta and induce thrombocytopenia in the fetus. The risk of this occurring is associated with the degree of depression of the platelet count but the relation is not absolute.⁴⁷ A positive platelet antibody test is found in about 75 per cent of patients but this test lacks specificity and is often difficult to perform in a setting of maternal thrombocytopenia. When the test is negative, one must depend on excluding other causes including P/E to make the diagnosis. Treatment with corticosteroids is the mainstay of

therapy. The recent introduction of high dose intravenous immunoglobulin (HDIVG) has proven useful in the management of cases refractory to steroids and for the acute preparation of a woman for delivery.⁴⁸ Whether HDIVG will raise the platelet count of the fetus is still uncertain.⁴⁹

3. Hemolytic Uremic Syndrome and Thrombotic Thrombocytopenic Purpura

Hemolysis is actually rare in patients with preeclampsia. In a subset of these patients renal failure will occur, particularly those with elevated liver enzymes, the so-called HELLP syndrome (hemolysis, elevated liver tests and low platelet count).⁵⁰ When renal failure is severe, the term "hemolytic-uremic syndrome" (HUS) is often applied to these patients although the pathogenesis of renal failure in the setting of preeclampsia is probably different from that of the more common HUS of childhood which occurs in infants and preschool children usually after a bout of gastroenteritis and often accompanied by bloody stools. Specific *E.coli* toxins seem to be responsible for the illness in children^{51, 52} while in the postpartum period it may be simply an extension of preeclampsia.⁵³ There are cases of postpartum HUS that occur months after delivery⁵⁴ and in these cases the pathogenesis may be unrelated to preeclampsia. Hormones are implicated in this rare syndrome since women taking conjugated estrogens⁵⁵ and oral contraceptives also have been reported with adult HUS.⁵⁶ Histologically there are glomerular and arterial microthrombi^{50, 57} and the peripheral blood displays characteristic microangiopathic changes. Clinically, the renal failure is associated with marked hypertension⁵⁸ and oligoanuria. Therapy is mainly supportive including short term hemodialysis if necessary. Plasma exchange may be useful in patients with convulsions or coma that is out of proportion to their degree of hyponatremia or uremia.⁵⁹

The distinction between post partum HUS and thrombotic thrombocytopenic purpura (TTP) may be difficult since both clinically and histologically they are quite similar. In general, the term TTP is used for patients with hemolysis, thrombocytopenia and renal failure in whom there is no known preeclampsia, a normal blood pressure,⁶⁰ and in whom the extra-renal manifestations are out of proportion to the renal failure. These patients often will have insufficient renal failure to justify hemodialysis although they may be profoundly ill with cerebral, cardiac and pulmonary complications of microthrombosis. In particular the cerebral symptoms dominate the

clinical picture and are often very fluctuant particularly early.

Treatment of TTP is best managed by prompt plasma administration and early plasma exchange.^{60a} The serum LDH is a good guide to therapy and levels <1000 units/dl usually are associated with marked improvement.^{60b} Steroids are used to diminish cerebral edema and perivascular inflammation and they seem to hasten the rise in platelet count. Steroids may be tapered in most patients soon after plasma exchange is instituted if the platelet count is >50,000/ul.

4. Lupus Anticoagulant

The lupus anticoagulant (LA) is an autoantibody that prolongs phospholipid dependent coagulation tests (prothrombin time, PT, and partial thromboplastin time, PTT). Although the clotting studies are abnormal, the LA is not associated with bleeding but with thrombosis.⁶¹ The presence of this autoantibody in a pregnant woman is an important marker for thrombosis⁶¹⁻⁶⁶ as well as recurrent first trimester fetal loss.⁶⁷ Several studies have demonstrated that plasma from patients with the LA inhibits the production of prostacyclin by vascular tissues.⁶⁸⁻⁷² Since production of prostacyclin by the endothelial walls is probably the most important mechanism for preventing platelet deposition and microocclusion, prostacyclin inhibition favors thrombosis and localized placental infarction.⁷³ Inhibition of prostacyclin production favors the development of P/E and also explains the high rate of preeclampsia and consequent fetal growth retardation that have been observed in pregnant women with an LA.^{66, 68, 74, 75}

Therapy with corticosteroids and low dose aspirin will reduce the rate of fetal loss. However, in a recent series of patients treated with this regimen,⁶⁶ preeclampsia developed despite suppression of the LA. Nearly two-thirds of fetuses experienced growth retardation. There is only a single case of thrombosis in the neonate associated with LA.⁶⁵ Heparin also has been used in these patients with some success^{67, 76} but to date there has been no controlled studies comparing aspirin and prednisone to heparin therapy. There was a recent report of a woman with the LA who had three successive fetal losses despite therapy with aspirin and prednisone and also heparin. She had a successful delivery by caesarean section, albeit in a setting of P/E, after repeated twice weekly treatment with high dose intravenous gamma globulin (HDIVG).⁷⁷ HDIVG merits fur-

ther study as primary therapy for parturient patients with LA and thrombocytopenia.

5. Thrombocytosis

Elevated platelet counts rarely complicate pregnancy and usually are due to myeloproliferative disease, either essential thrombocythemia or polycythemia vera.⁷⁸ While the experience with such patients has been generally good, platelet counts above $1 \times 10^6/\text{ul}$ are associated with occasional catastrophes⁷⁸ and it is prudential to lower the counts with plateletpheresis immediately before delivery. The role of anti-platelet agents or chemotherapy in this setting is uncertain.

II. Coagulopathy Primarily Related to a Disturbance in the Clotting Mechanism

The above disorders are characterized by activation and consumption of platelets and conceptually are unified by studies of prostaglandin metabolism that give some insight into the role of the platelet and endothelial cell in pathogenesis of the microthromboses that occur in many of these disorders.³⁰ The group of disorders that follow are characterized by a major activation of the intravascular clotting mechanism and secondary thrombocytopenia. These states are characterized by abnormally prolonged coagulation tests (PT and PTT), low fibrinogen, FVIII and FV levels as well as the appearance in the circulation of fibrin degradation products (FDP) and the appearance of the D and dimerized D fibrin fragments in the circulation. In severe cases the venous blood may be virtually incoagulable, and severe hemolysis and hemoglobinemia and hemoglobinuria occur. The microscopic appearance of the blood is dominated by severe schistocytosis and secondary thrombocytopenia.

1. Abruptio Placentae

Premature detachment of the placenta with the formation of a retroplacental hematoma is the most common cause of acute coagulopathy in the parturient and occurs in about one per cent of all deliveries. Although it is rare for the mother to die, fetal mortality is high.^{79, 80} The reason for the relatively low maternal morbidity is the availability of blood transfusion. The history of modern blood transfusion may be thought of as having started in 1824 with the work of the British obstetrician James Blundell, who reported that five of eight women transfused with blood, following a severe post-partum hemorrhage, survived at a time when the mortality in this setting approached 100 per cent.⁸¹ Severe blood loss may

Table 3 — Disorders Primarily Related to Activation of Clotting Proteins

- 1 Abruptio placentae
- 2 Amniotic fluid embolism
- 3 Intrauterine fetal death
- 4 Infection

occur since the blood flow through the uterine arteries at the time of delivery is 600-800 ml/min.⁸² The mainstay of treatment is volume replacement.^{83, 84} With tetanic uterine contractions, a vicious cycle of increasing hemorrhage and hypotension occurs, ultimately culminating in fetal death. In virtually all fatal cases there is a severe consumptive coagulopathy (DIC) and they bleed freely from any break in the circulation. The mainstay of therapy is platelets and fresh frozen plasma in large volumes and additional administration of cryoprecipitate to raise the fibrinogen levels. While stabilization of the patient is crucial, delivery should not be delayed unnecessarily in a prolonged effort to completely reverse the coagulopathy. If vaginal delivery can not be achieved in a short time, a caesarean section should be performed even if fetal demise has occurred.⁸³ Continued transfusion support should be given after the delivery and usually hemostatic abnormalities return to normal within a day although it is not uncommon for thrombocytopenia to persist for a few days.

2. Amniotic Fluid Embolism

Amniotic fluid embolism (AFE) is an obstetrical catastrophe which accounts for 10-20 per cent of all maternal deaths^{84, 85} and is the leading maternal cause of death at the time of delivery.⁸⁶ Labor has commenced in at least 80 per cent of patients who experience an AFE at a time when engagement of the fetal head in the cervical canal may block drainage of the amniotic fluid.⁸⁷ Nevertheless, a substantial proportion occur with intact membranes and even have been thought to have occurred during first trimester abortions.⁷⁸ The diagnosis is suspected when a woman in active labor suddenly experiences respiratory difficulty, followed by rapid cardiopulmonary collapse. At least a quarter of patients rapidly develop intractable shock and die in the first hour.^{84, 86} The remainder stabilize to some degree and in these patients a severe coagulopathy develops, characterized by markedly prolonged PTT and the appearance of thrombocytopenia. AFE patients typically have extremely high levels

of FDP reflecting a markedly augmented fibrinolytic activity.^{86, 87} The acute DIC is caused mainly by the direct activation of the intrinsic pathway by the powerful thromboplastic activity of the amniotic fluid. The diagnosis can be confirmed by the detection of amniotic fluid in the maternal venous blood.⁸⁸⁻⁹¹

Treatment is supportive and is aimed at providing support of the blood volume with transfusions of packed cells and vigorous colloid resuscitation. Ventilatory assistance is required in all patients. Transfusion therapy for the coagulopathy should include large volumes of FFP and cryoprecipitate. As much as 20 units of each may be required for the first few hours. Pulmonary edema may develop with this therapy and should be treated with diuretics. As quickly as possible, delivery should be accomplished, even by caesarean section (if necessary), since bleeding only worsens over time if the delivery is delayed. The mortality quoted in the literature is over 80 per cent,⁹² but in one recent small series the mortality was less than 30 per cent,¹² indicating that prompt recognition, improved intensive care and transfusion support will save lives.

3. Septic Shock

Sepsis and shock may cause a DIC to develop in up to half of the cases.⁹³ Urinary tract infection, chorioamnionitis and endometritis have been the underlying site of sepsis in most patients. The latter used to be particularly common as a sequelae to criminal abortion because of the lack of sterile technique and the often primitive means used to induce the abortion (eg coat hangers). In patients who develop a DIC there has been a large exposure to endotoxin, which activates the complement cascade and intrinsic pathway of coagulation simultaneously.⁹⁴ Platelets are also aggregated leading to the formation of microthrombi. The observation of a fully developed DIC with defibrination has an ominous prognostic relevance and the mortality can approach 95 per cent if renal failure also supervenes.⁹⁵ Because the offending pathogens may be aerobic or anerobic, gram positive or gram negative, it is important to initiate therapy with a combination of potent broad spectrum antibiotics. Therapy for the coagulopathy is usually not as difficult as for an AFE and treatment with FFP and platelets (if the platelet count is below 50,000/ul) will often correct the coagulopathy. Caution should be observed in using platelets in the first few hours since endotoxin may be further liberated by the action of the antibiotics and probably

should be avoided unless the patient is actively bleeding. In severe cases, heparin will terminate the DIC related to sepsis but should be reserved for the patient with diffuse bleeding intractable to FFP and platelet therapy. If sufficiently vigorous measures have been taken to stabilize the patient and shock continues, the uterus should be emptied. If shock continues after delivery a hysterectomy should be considered.

4. Retained Dead Fetus

Intrauterine death will be followed by defibrination in about one-third of cases if the fetus is not removed within a month of its demise. This comes about as a result of a chronic DIC triggered by the slow release of tissue thromboplastin from the macerated fetus. Although the fibrinogen level is usually very low, there is little evidence of bleeding in this situation, presumably because the kinetics of the clotting factor consumption are slow and the liver removes the activated factors as they form. Coagulation tests often show the other clotting factors to be normal. Supportive therapy is usually not needed and the uterus can be evacuated safely if there has been no signs of vaginal bleeding. In the unusual event of a single fetal demise in the case of a multiple pregnancy, it is possible to treat the patient with heparin and ablate the chronic DIC, allowing the pregnancy to progress to the point where the viable fetus can be safely delivered.⁹⁴ Heparin is usually given subcutaneously, but if intravenous heparin is required, an insertion of a Hickman catheter and ambulatory management is preferable to prolonged hospitalization.⁹⁶ If available, low molecular weight heparin is preferable to standard heparin, since it has a longer half life and does not decrease antithrombin III.⁹⁷

Summary

Normal pregnancy is characterized by a hypercoagulable state that may progress to large or small vessel thrombosis and in some situations terminate in gross bleeding, due to consumption and lysis of clotting factors. Recent information concerning alterations in the factors that control normal clotting has helped in the identification of individuals at special risk for clotting and bleeding problems. At the present time, transfusion support is limited to unfractionated or semi-fractionated blood products. As knowledge is advanced, recombinant blood derivatives that will eliminate the risk of transmission of disease in the transfusion management of bleeding patients will emerge. In many patients consumption and

lysis of clotting proteins occurs in catastrophic situations. In these situations the good clinical judgement of the obstetrician is of paramount importance. In order for the obstetrician to exercise this judgement most effectively, there must be good lines of communication among the clinicians involved in the patient's care and prompt, responsive support from the coagulation laboratory and the transfusion service.

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Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral alpha-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

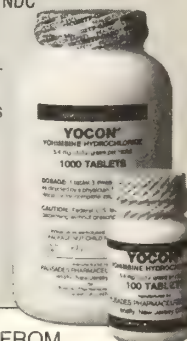
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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BRIEF SUMMARY

CONTRAINDICATIONS

There are no known contraindications to the use of sucralfate

PRECAUTIONS

Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration.

Drug Interactions: Animal studies have shown that simultaneous administration of CARAFATE (sucralfate) with tetracycline, phenytoin, digoxin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. This interaction appears to be nonsystemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The clinical significance of these animal studies is yet to be defined. However, because of the potential of CARAFATE to alter the absorption of some drugs from the gastrointestinal tract, the separate administration of CARAFATE from that of other agents should be considered when alterations in bioavailability are felt to be critical for concomitantly administered drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted.

Pregnancy: Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients treated with sucralfate, adverse effects were reported in 121 (4.7%).

Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

OVERDOSAGE

There is no experience in humans with overdosage. Acute oral toxicity studies in animals, however, using doses up to 12 gm/kg body weight, could not find a lethal dose. Risks associated with overdosage should, therefore, be minimal.

DOSAGE AND ADMINISTRATION

The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

HOW SUPPLIED

CARAFATE (sucralfate) 1-gm tablets are supplied in bottles of 100 (NDC 0088-1712-47) and in Unit Dose Identification Packs of 100 (NDC 0088-1712-49). Light pink scored oblong tablets are embossed with CARAFATE on one side and 1712 bracketed by C's on the other. Issued 1/87

Reference:

1. Eliakim R, Ophir M, Rachmilewitz D: *J Clin Gastroenterol* 1987;9(4):395-399.

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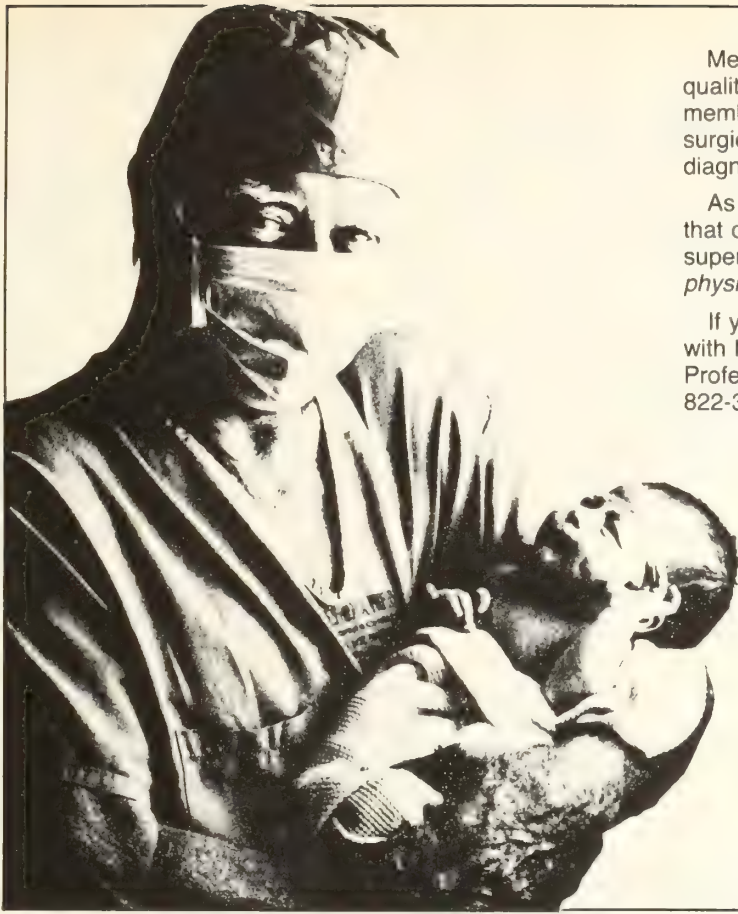
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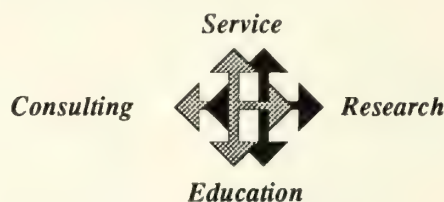
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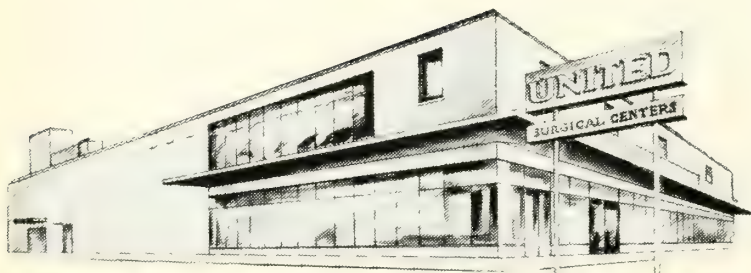
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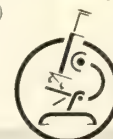
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Recent Abstracts of Interest

Capsule Comments on Maternal-Newborn Health Problems

Cocaine Has Major Implications for Mother and Neonate

Cocaine abuse during pregnancy has been associated with a variety of possible complications to the developing fetus. This study compared two cohorts of mother-infant pairs, one group of 53 mothers who reported using cocaine during pregnancy and one who did not. Controls were a random sample of 100 patients from the same hospital population. Adverse effects associated with cocaine involved both mother and infant. Significantly more pregnancies of abusers were associated with pre-term labor (11 vs. 2), and pregnancy-related hypertension (13 vs. 4). Newborn infants of abusers had a greater frequency of meconium (13 vs. 4), tachycardia (10 vs. 2), as well as an increased risk of seizures and hyper-responsiveness. Major congenital abnormalities were significantly increased in frequency among infants of mothers who had used cocaine including two cases of ventricular septal defect, one of atrial septal defect, and one of cardiomegaly.

Other studies have reported that infants born to mothers who abuse cocaine have reduced mean birth weight, reduced head circumference, and an increased risk of prematurity. Placental vascular abnormalities such as placental abruption or placenta previa may be increased with cocaine use as is stillbirth. This is a study from an inner-city hospital in Dallas, Texas, treating mainly indigent patients. An inherent problem in design might be related to self reporting of substance abuse and possible confounding variables such

as other drug use, including tobacco or alcohol in the two groups as well as differing nutritional status. These variables were not assessed.

Little BB, Snell LM, Klein VR, et al: Cocaine Abuse During Pregnancy-Maternal and Fetal Implications. *Obstet Gynecol* 73:157-160, 1989.

Screening for Hepatitis B in Pregnant Women May Not Identify a Majority of Infected Individuals

Screening for Hepatitis B surface antigen was performed in 4,399 consecutive pregnant women to assess the sensitivity of historical risk factors for transmission of perinatal infection of the Hepatitis B virus. Twenty-three positive women were identified (5.2 per 1,000 deliveries). Hepatitis B surface antigen positivity was significantly increased in women from Black, Hispanic or Asian ethnic groups. Only 10 of the 23 asymptomatic carriers had risk factors as previously defined for Hepatitis B infection (including women of Asian, Alaskan, Sub-Saharan or Eskimo origin, history of acute or chronic liver disease, work or treatment in dialysis units or institutes for the mentally retarded, rejection as a blood donor, repeated transfusions, frequent occupational exposure to blood, household contacts of Hepatitis B carriers, multiple episodes of venereal disease, and intravenous drug abuse history).

The sensitivity of detection was low. Factors cited may be failure to obtain a detailed history, reluctance of subjects to give a history of venereal disease or drug use. Some authorities argue that

only routine Hepatitis B surface antigen screening of pregnant women will achieve effective immunoprophylaxis of newborn children, most of whom will become Hepatitis B carriers if infected. Others argue that universal screening would produce a major incremental increase in cost to detect infants of mothers not known to be in a high-risk group or at hospitals not serving a large immigrant or low socioeconomic clientele. The opposing view is that some studies have clearly indicated that high-risk pregnancies account for only about half of all Hepatitis B surface antigen positive women.

Kumar ML, Dawson NV, McCulloch AJ, et al: Should All Pregnant Women be Screened for Hepatitis B? *Ann Int Med* 107:273, 1987 and Stevens, CE. Perinatal Hepatitis B Virus Infection — Screening of Pregnant Women and Protection of the Infant: *Ann Int Med* 107:413, 1987.

Immunoprophylaxis Reduces Risk of Perinatal Hepatitis B Virus Infection

Current evidence suggests that 70-90 per cent of infants born to Hepatitis B surface antigen positive and e antigen positive mothers will be infected with Hepatitis B virus and become chronic carriers. Reduction in risk to infants has been documented with a combination of Hepatitis B vaccine and Hepatitis B immunoglobulin in the neonatal period. A new yeast-recombinant Hepatitis B vaccine has been developed and was compared to a plasma-derived vaccine in 122 high risk newborns of Asian-American women. All mothers were Hepatitis B carriers and e antigen-positive at the time of delivery. Only 4.8 per cent of infants who received Hepatitis B immunoglobulin and yeast vaccine became carriers compared to 10.2 per cent who received a plasma-derived vaccine and immunoglobulin. This study is useful since it supports the efficacy of immunoprophylaxis in high risk newborns and indicates that the recombinant vaccine is an alternative to a plasma-derived product.

Another approach has been suggested in hyperendemic areas since maternal-neonatal Hepatitis B transmission perpetuates the viral carrier state. Though inappropriate in areas with low Hepatitis B virus prevalence, universal immunization of newborns might be practical if an effective, inexpensive vaccine were available for mass use in areas where Hepatitis B is endemic.

Stevens CE, Taylor PE, Tong MJ, et al: Yeast Recombinant Hepatitis B Vaccine — Efficacy With Hepatitis B Immunoglobulin in Prevention of Perinatal Hepatitis B Virus Transmission. *JAMA* 257:2612, 1987.

Edited by Edward R. Feller, MD



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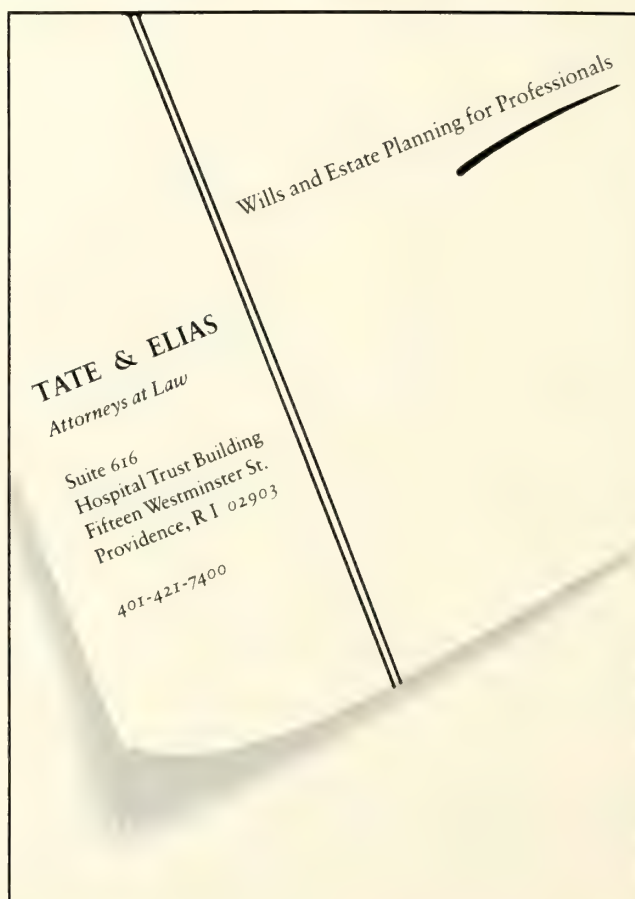
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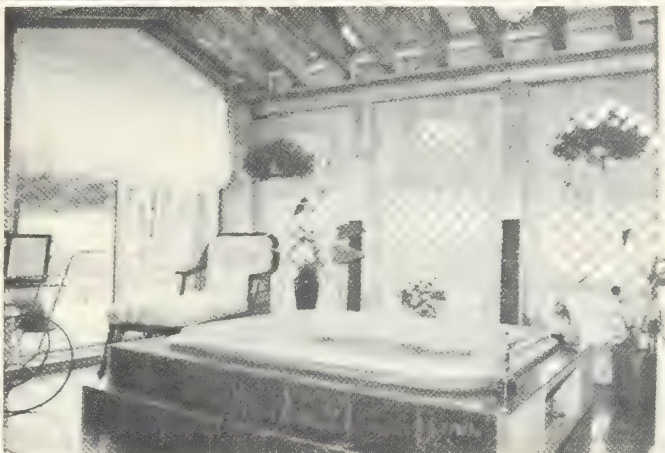
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Contraindications: VASOTEC[®] (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Warnings: **Angioedema.** Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Heart failure patients given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy (See DOSAGE AND ADMINISTRATION). Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in heart failure patients), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: **General:** **Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: Elevated serum potassium (> 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See Drug Interactions.)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema. Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia. Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Hypotension: Patients on Diuretic Therapy. Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methylglucoside, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium: A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. Although a causal relationship has not been established, it is recommended that caution be exercised when lithium is used concomitantly with VASOTEC and serum lithium levels should be monitored frequently.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters.

There are no adequate and well-controlled studies in pregnant women. VASOTEC[®] (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Milk in lactating rats contains radioactivity following administration of ¹⁴C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 298/ patients.

Hypertension: The most frequent clinical adverse experiences in controlled trials were headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

Heart Failure: The most frequent clinical adverse experiences in both controlled and uncontrolled trials were dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

Cardiovascular: Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, Hypotension), cardiac arrest, pulmonary embolism and infarction, rhythm disturbances, atrial fibrillation, palpitation.

Digestive: Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis.

Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), prostate hypertrophy.

Respiratory: Bronchospasm, rhinorrhea, asthma, upper respiratory infection.

Skin: Herpes zoster, pruritus, alopecia, flushing, photosensitivity.

Other: Muscle cramps, hyperhidrosis, impotence, blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include fever, myalgia, and arthralgia, an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Clinical Laboratory Test Findings

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol%, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

Dosage and Administration: **Hypertension:** In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed. If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Hypertensive Patients with Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure: VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects.) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

Dosage Adjustment in Heart Failure Patients with Renal Impairment or Hyponatremia: In heart failure patients with hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine > 1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, Heart Failure, WARNINGS, and PRECAUTIONS, Drug Interactions.) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

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The Elderly and Their Environment

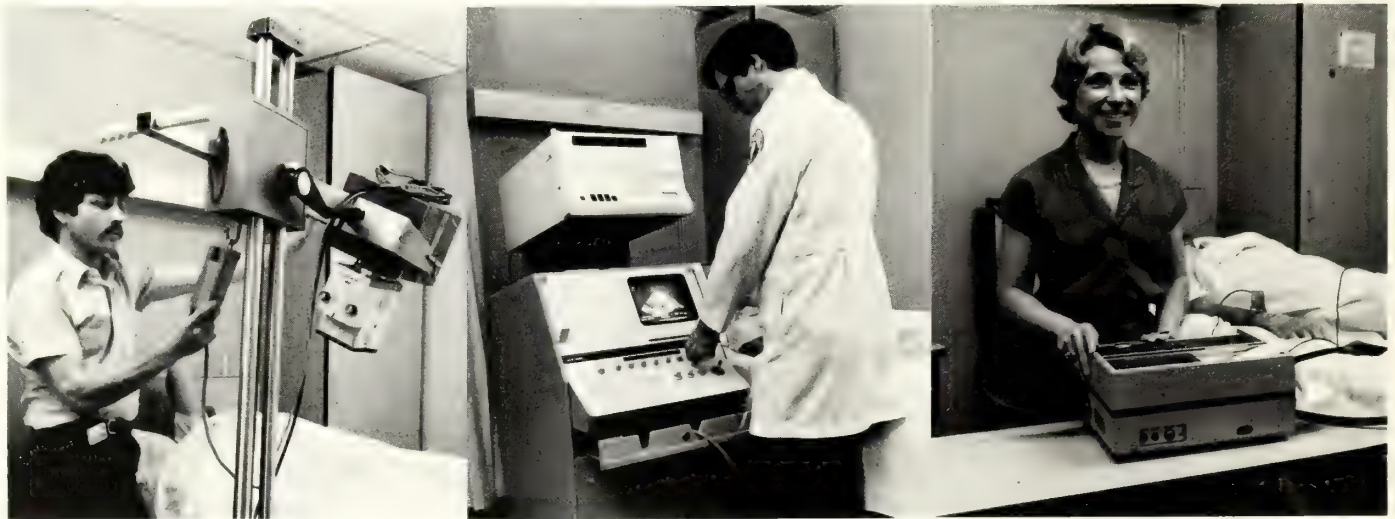
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It is rarely desirable to include a complete review of the literature in the references. An alphabetized bibliography is to be used only when the listing is of books suggested for supplementary reading.

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Cover: Cover photo by David H. Leach is an example of most nursing home corridors. See page 161.

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The Shrinking Sensory World of the Elderly

As she carefully makes her way down the corridors of gleaming patterned floor-tile, the old woman grasps the handrail tightly. Bright sunlight streams through the window at the end of the hallway, producing shadows and creating sharp contrasts. A few wheelchairs line the corridor; an employee mops the floor and places the "wet floor" sign as a warning. A loudspeaker overhead announces a meeting downstairs, and then a physician is paged. The beige wallpaper is matched to the yellow-grey floor. A painting of bright flowers hangs on one wall.

This scene is typical of most nursing home corridors and illustrates the meager attention we pay to the sensory experiences of the elderly housed and cared for in our extended care institutions. The sunlight pouring through the window at the end of the corridor is blinding; the different colors of the floor tiling are seen as separate levels up and down; the floor and the walls appear to blend together seamlessly; and wheelchairs, bins and other items represent obstacles that must be negotiated. The loudspeaker interrupts, yet the words cannot be distinguished. And to this frail 87-year-old woman with Alzheimer's disease, the bright painting on the wall seems to frame menacing and frightful flames.

We are an aging population and our state now has one of the highest proportions of elderly in the nation. Our ten thousand nursing home beds are many times the number of our hospital beds and are currently occupied by one Rhode Islander in every ninety-five. Further, over half of this nursing home population suffers from some measure of enduring, organic dementia.

The Jewish Home, one of the largest nursing centers for the aged in Rhode Island, has recently assembled a working committee to study the problems of nursing home ambience and then to seek feasible solutions. This committee of seventeen (architects, interior decorators, industrial

designers, nursing home administrators, social workers, physical therapists, social scientists, nurses and physicians) is attempting to understand how an ostensibly efficient physical environment designed for a younger population interacts with the sensory and cognitive impairments of the elderly. The ultimate goal of the committee is to find ways of diminishing the emotional and physical threat which an indifferently planned environment may impose on the elderly, and at the same time increase for them the elements of privacy, individuality and autonomy.

The committee has identified four arenas of initial inquiry:

- 1) *Bedrooms* — their design, safety features and contained furniture
- 2) *Corridors* — particularly the perceived sensory and physical menaces and their solutions
- 3) *Public Spaces* — particularly social, dining, recreational and therapy sites
- 4) *Restraints* — the design, appropriateness and means by which they are employed

From time to time the *Rhode Island Medical Journal* will offer papers which address these issues. The first of these is authored by Professor Mary Kalymun of the University of Rhode Island and discusses sensory changes accompanying the aging process, and then proposes simple, low-cost living space adaptations which can assist the elderly in maintaining a greater measure of serenity and independence.

Renée Rose Shield, PhD
Director of Research and Education
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Clinical Instructor
Department of Community Health
Brown University, Providence, Rhode Island

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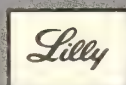
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2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency.

3. Pharmacokinetic studies in patients with hepatobiliary syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

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Drug Interactions — No interactions have been observed between Axid and theophylline, chlorazepate, lorazepam, lidocaine, phenytoin and warfarin. Axid does not inhibit the cytochrome P-450 linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility — A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a two-generation, prenatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy — Fetalogic Effects — Pregnancy Category C — Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spinal brida, hydrocephaly, and enlarged heart of one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers — Studies conducted in lactating women have shown that < 0.1% of the administered oral dose of nizatidine is secreted in human milk in proportion to plasma concentrations. Caution should be exercised when administering nizatidine to a nursing mother.

Pediatric Use — Safety and effectiveness in children have not been established.

Use in Elderly Patients — Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions — Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. Domestic placebo-controlled trials included over 1,300 patients given nizatidine and over 1,300 given placebo. Among reported adverse events in the domestic placebo-controlled trials, sweating (1% vs 0.2%), urticaria (0.5% vs < 0.01%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A variety of less common events was also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic — Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients and was possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L), and, in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular — In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

CNS — Rare cases of reversible mental confusion have been reported.

Endocrine — Clinical pharmacology studies and controlled clinical studies showed no evidence of antiandrogenic activity due to Axid. Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo. Rare reports of gynecomasia occurred.

Hematologic — Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H₂-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental — Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity — As with other H₂-receptor antagonists, rare cases of anaphylaxis following administration of nizatidine have been reported. Because cross-sensitivity in this class of compounds has been observed, H₂-receptor antagonists should not be administered to individuals with a history of previous hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other — Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine administration have been reported.

Overdosage — Overdoses of Axid have been reported rarely. The following is provided to serve as a guide should such an overdose be encountered.

Signs and Symptoms — There is little clinical experience with overdosage of Axid in humans. Test animals that received large doses of nizatidine have exhibited cholinergic-type effects including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous median lethal doses in the rat and mouse were 301 mg/kg and 232 mg/kg, respectively.

Treatment — To obtain up-to-date information about the treatment of overdose, a good resource is your certified regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the Physicians' Desk Reference (PDR). In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance.

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Relationships Between Sensory Decline Among the Elderly and the Physical Environment: Implications for Health Care

Maximizing the Wellbeing of the Elderly Through Environmental Change is of Great Importance

Mary Kalymun, PhD

Introduction

By the year 2000, elderly people will outnumber younger people, and the total nursing home population will rise by 54 per cent.¹ Will their residential settings suggest that aging is a disease or that it is a normal part of life to be experienced to the fullest? As medical care providers and others understand the nature of age-related changes and the extent to which the physical environment enables or impedes health care, it follows that the quality of life during the later years will be optimized.

The elderly are a most heterogeneous population in physiological, psychological, and social capabilities. Therefore, it is difficult to describe them in terms of specific competencies.² While studies have shown that elderly people are quite competent, the fact remains that the incidence of disability and chronic disease increases with chronological age.³

It is universally known that sensory abilities diminish with age. However, elderly people vary in terms of the type of sensory loss they develop

and the extent to which it occurs. For example, one person may hear well but have limited visual acuity while another may hear poorly and see well.

Multiple sensory handicaps are the rule rather than the exception⁴ and they may occur either gradually or abruptly. Most often, they have their beginnings in the years between ages 40 and 50, not usually having significant impact on behavior until after the age of 60.⁴ Although elderly people learn how to adjust and compensate for these changes, sensory deficits become more severe with time. By the late 70s or early 80s, losses may become serious enough to interrupt daily functioning. Ability to adjust at this point becomes more critical if the individual is to sustain and maximize independence. In instances where sensory changes are less gradual, feelings of depression, anger, and hostility are commonly expressed and the willingness to adjust is limited.

Adjustments to sensory change are made easier through adaptive environmental design in both private and public settings.⁵ Dr Powell Lawton, of the Philadelphia Geriatric Center, maintains that institutional settings which have stimulating qualities can penetrate these higher sensory thresholds, and improve the level of functioning more than proportionately.³ Furthermore, it is suggested that total wellness is dependent upon favorable environmental conditions.⁶

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Problem Statement

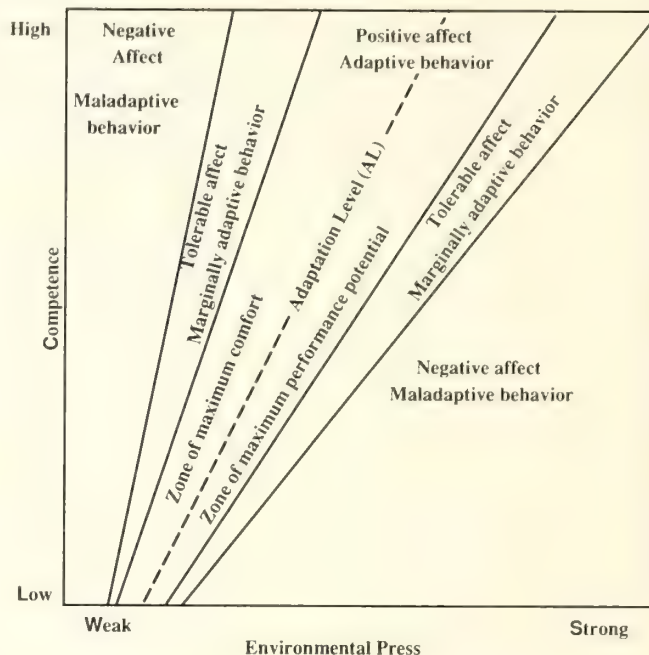
It has been reported that sensory impairment can sometimes be mistaken for cognitive deficits during later life.⁷ Consequently, it is imperative to understand the nature of sensory loss, and characteristics of the physical environment that aggravate or compound this situation.

It has been said that "thoughtless environmental design 'speaks' to people with sensory losses, telling them that they are incapacitated, senile, slow, weak, and perhaps too stupid to survive."² Therefore, the purpose of this paper is to elaborate on sensory decline in later life and discuss interactions between it and characteristics of the physical environment that impact on well-being.

Theoretical Perspectives

The physical environment is constantly with us, irrespective of developmental stages and, as functional human beings, we continuously interact with it. The first psychologist to conceptualize a relationship between individuals and their environment was Kurt Lewin. He maintained that behavior is a function of people and their environment. Although his theory is logically convincing, it is too broad to be tested since what constitutes the person and the environment is unspecific. Lewin's thinking is echoed in the gerontological literature through the environmental docility hypothesis which maintains that the less competent the individual the greater the impact of the environment on the person.³ Further elaboration on Lewin's thinking was generated through Lawton and Nahemow's ecological model of competence and environmental press (See Figure 1). This model associates the person with competencies in the biological, sensorimotor, cognitive and ego strength domains, and the environment with the demand character of the physical milieu, referred to as press. The ecological model maintains that results of interactions between individual competence and environmental press can be placed on a continuum from positive to negative and are manifested on two levels, as affect and behavior. Where competence and press are in balance, adjustment prevails resulting in positive affect and adaptive behavior. In the zone of maximum performance where press level increases, the individual is motivated to use personal competence to the fullest. In the zone of maximum comfort where "reduced motivation, mild dependence, and passive enjoyment"³ is experienced, press level decreases. Affect and behavior in both of these zones

Fig 1. Ecological Model. (Reprinted with permission from "Environment and Aging," by M.P. Lawton. Copyright 1980 by Brooks/Cole Publishing Company, Monterey, CA.)



are positive. Beyond the limit of these zones tolerable affect and marginally adaptive behavior exist. This is where individuals are clearly uncomfortable with the environment and are barely tolerating it. If the gap between levels of competence and environmental press continue to expand, negative affect and maladaptive behavior result. This is to say that everyone reaches a breaking point.

In general, the ecological model maintains that the higher one's competence, the higher the range of press one is able to tolerate and vice versa. Regardless of the situation, balance between competence and press generates positive affect and behavior while extreme imbalance generates negative results.

A second theory that focuses on relationships between elderly people and their environment is Kahana's congruence model of person/environment interaction.⁸ The congruence model considers individual needs and preferences (parallel to the concept of competence in the ecological model) vis-a-vis environmental factors on well-being of older adults.

Kahana delineated seven dimensions of necessary congruence between elderly individuals and residential settings. These dimensions are examined on a parallel basis whereby individual characteristics are based upon changing needs

and preferences, and environmental characteristics are related to the degree of control the environmental setting has over individuals. Both constituents are considered simultaneously as parallels in examining congruence (synonymous to the concept of adjustment in the ecological model) between individuals and their residential milieu.

Kahana maintained that the goodness of this fit is preliminary to well-being but not synonymous with it. If dissonance prevails between the individual and the environment, stress and discomfort become apparent. In this event adaptive strategies are in order whereby individuals or the environmental setting must adjust. The success of these adjustments results in well-being or the lack of it (ie, a positive or negative mental state).

Person-environment congruence in residential settings is especially important when older adults are subject to declining physical resources and are limited in their options to choose living arrangements that meet their needs. If the residential setting is such that it restricts sensory stimulation in the immediate environment, the individual is less able to exercise control.

Sensory Loss

With advancing age, sensory impairment alters one's perception of the environment. Problems evolve in relation to understanding it. The following discussion will elaborate on sensory loss and ways in which characteristics of the physical environment may prevent or facilitate well-being.

Vision

Changes in vision and hearing are the most widespread sensory impairments. Twenty-five per cent of people in nursing homes are considered legally blind and another 35 per cent have impaired vision.⁴ Changes in visual acuity develop as the lens of the eye thickens and becomes opaque. Loss of ability to see fine detail begins in the forties.^{4,5} Individuals express difficulty in recognizing objects, threading a needle, and being able to read fine print. While the height of letters needs to be raised, the width between their spacing also needs to be increased.⁵ This becomes especially helpful in reading prescriptions and dietary menus.

Yellowing of the lens impairs color vision in that violets, blues, and greens fade out of the color spectrum^{7,9} with limited effect on ability to discern red, orange, and yellow. Experimenters can simulate this color change by looking through yellow acetate sheets.

Color contrast is used to avoid accidents since boundaries are difficult to distinguish when various shades of the same hue (color) are placed next to each other. For example, a light green wall and a blue green rug become impossible for an elderly person to distinguish and stumbling into the wall is common.² Although a whole world of black and white is certainly impractical, wherever appropriate, enhanced contrast is helpful for the visually impaired. Signs with black background and white lettering or symbols are most effective⁹ in identifying location points in a building. Also, the use of graphics to replace words is helpful. When a resident in a shared living facility is on route to the dining room, a graphic sign, hung perpendicular to the entry of the room and showing a place setting or eating utensils, can be seen from a distance and is reassuring to the traveler. In addition to color, visual contrast can be amplified through the use of texture, objects, and finishes.⁶

Another common concern about the visual environment of older people is inadequate light. As the pupil of the eye decreases in size there is a need for more light. Translated into physical environment terms, the average 80 year old needs three times as much light to see with the same clarity as a twenty year old.¹⁰ If light levels in institutional settings are inadequate, elderly people tend to be passive or uninvolved rather than to participate in both individual and shared activities. Task lighting, produced by table and floor lamps, track lights, and daylight, is a solution for producing high light intensity for reading, writing, and other such endeavors.

It takes longer for an elderly person's eyes to adjust when moving from one space to another where there is a significant difference in light intensity (ie, moving from a lighted foyer to a darkened theater). Once the transition has been made the elderly person is able to see less than a young person in the darkened area.

Evenness of illumination is an aspect of lighting which warrants special consideration, since the absence of it can create increased vulnerability to accidents. When elderly people move during the night from a dark area to a lighted area, their eyes are likely to play tricks on them. Instead of understanding the floor to be level at the juncture of the bedroom and the hallway, it is perceived as a step. Therefore, an inappropriate adjustment of body weight can precipitate a fall. This type of situation can exist when walking from a dimly lit waiting room to an examining office or when traveling in a poorly lit hall-

way where sources of light are spread so far apart they create a situation of continuous movement from light to dark areas. In the first instance intermediate lighting is necessary to facilitate a transition from a dimly lit waiting room to a highly lit examining room. In the second instance sources of light need to be more closely spaced in a hallway to permit an evenness of light intensity. Uniform lighting is extremely important to decrease accidents and allow for easier negotiation of the environment.⁵ Floral carpeting should be avoided on stairs since it makes it more difficult to judge either the height or the edge of a step, when the patient has an altered depth perception.⁹

Research shows that light fixtures such as sconces and chandeliers, with clear glass bulbs and visible filaments, deteriorate the retina of older people.⁶ Yet, most of my professional travels have taken me from one place to the next where such fixtures are often used to create a dignified attitude in the facility. These fixtures are purely decorative and should not be expected to produce adequate amounts of light for the elderly negotiating the environment or engaging in focused activity. If used at all they should be accompanied by frosted low wattage bulbs or lens covers which reduce the potential danger to the retina. Also, it is suggested that they be installed with dimmers.

Fluorescent lamps, commonly used in institutional settings, cause visual discomfort to the elderly who are sensitive to a subtle light flicker that often comes with fluorescent lighting. Other reactions to fluorescent lighting include tearing, elevated stress level, headache and inattentiveness. It is suggested that full spectrum lamps which simulate the full color and spectrum of sunlight be used. Full spectrum light is known to increase visual acuity, reduce fatigue, and even increase intestinal calcium adsorption.⁶

A discussion of common problems affecting the visual environment of elderly people would be incomplete without mention of the issue of glare. As the aging human lens becomes more dense, light is scattered, producing a sensation of glare, an uncomfortable brightness producing interference in vision. Glare causes discomfort, tearing, and headache. Prolonged exposure elevates stress in the elderly, which places the body in a defensive mode and fosters reduced attention and loss of memory. With elevated stress levels people become irritated and short-tempered.⁵

Glare is a problem at night for older drivers.

It makes boundaries and edges more difficult to perceive. Steps in bright sunlight blend together and the height of a curb fades into the street.⁵ The white background of traffic signs creates glare. In order to counteract glare, edges need to be made clearer by choosing a color in contrast with the color of the background surface.⁵

The reduction of glare in institutional settings is of paramount importance. Glare is everywhere, on table tops, silverware, wallhangings, magazines, etc. It is especially pronounced with highly polished floors and vinyl upholstery. Ways to control glare include the use of carpeting, fabric upholstery, tablecloths, and balanced artificial light as opposed to a single source of illumination.

Types of glare differ in that they are either direct or reflective. Direct glare is caused by a light source which is relatively easy to control by blocking it out with shades, curtains, or overhangs. Reflective glare is a more complex problem in that the source of reflection may not be as easily eliminated when caused by room finishes, height of the ceiling, the placement of light fixtures or windows, and other factors difficult to rectify.

Hearing

A decline in the ability to hear affects more elderly people than any other single chronic condition.⁴ Fewer than 12 per cent of those over 65 years have normal hearing and between 30 per cent and 50 per cent have hearing loss that significantly affects communication and relationships with others.⁴ People in general are less understanding and patient with individuals who have a hearing loss, than with those who have lost their vision.

Hearing is crucial to mental health in later life.⁷ Inability to hear tends to generate depression and paranoid states, and causes greater social isolation than blindness.⁷ More older men than women are affected by this sensory loss resulting from cumulative insults over a person's lifetime. In the case of men it is hypothesized that the environmental nature of their past work settings is largely responsible for their hearing loss.

Some people accept their auditory loss by wearing a hearing aid. Others deny that a problem exists. A willingness to accept general amplification of all sounds in the environment is a trade-off for not being able to hear. A hearing aid does not have a mind that discriminates between sounds nor is it able to select which sounds

to turn off and which to amplify in accordance with personal choice.

An inability to hear high frequency sounds (presbycusis) is a common occurrence during late adulthood. Since consonants (ch, sh, s, z, f, p) in the English language are located in the high frequency range, speech is frequently inaudible.⁴ I remember shopping for a grandfather's clock as a gift for my parent's 50th wedding anniversary. The basic criterion for selection was the pitch of the chimes, the lower the better. The gift was a hit! Four years later they continue to enjoy the ambience it creates for auditory gratification, in spite of their hearing deficits. I remember reading about organ music having a similar affect on elderly people because of its low frequency range.

There are instances in which elderly people are able to hear high frequency sounds but are unable to understand speech because of a neural problem that exists in the transmission of sound between the ear and the brain.⁵ This situation is exacerbated when trying to follow a conversation involving several people (ie, family gatherings, parties), and in the presence of background noise as generated by appliances and air-conditioning units.

Inability to hear creates stress which leads to discomfort, increased blood pressure, shortened attention span, headache, and apparent loss of memory. Furthermore, intelligibility drops as levels of stress increase for the listener.⁶

Physicians and other health care providers are encouraged to act on this information as they attend to the medical needs of elderly people. Being hospitalized or making an office visit is stressful enough for people concerned with their impending health status, notwithstanding their inability to hear. Patients are unable to hear if the attending physician is not looking directly at them. Adequate light is essential to see facial expressions and to allow for lip reading. Using distinct pronunciation, slowed speech, and a somewhat louder voice is essential. Furthermore, elderly people need to be told when there is a change in conversation to avoid confusion.⁵ They should be encouraged to ask for repetition of information for better understanding of it.

Be aware of the affect of background noise on one's inability to hear. The presence of music will make speech hard to understand. Attention to the acoustical qualities of the environment is essential. Open office spaces invariably create problems. Rooms used for conversation need to be separated from noisy areas. Noise can be controlled through the use of carpeting on two walls

or on one wall and the ceiling. Likewise, draperies hung over glass surfaces are effective in controlling high frequency ranges.⁶

In consideration of residential settings other environmental recommendations become apparent. The use of public telephones with amplification devices are necessary. Canned music is potentially distressing to the sensory impaired person since it creates a uniform environment dampening characteristic sounds that serve to identify a place (ie, kitchen, dining room, living room).

Middle frequency auditory signals should be used to back up visual signs. For example, while an elevator indicates visually what floor it is on, it may simultaneously sound a middle range tone to serve as redundant cueing for the resident. This is most appropriate for buildings with six floors or less.

Tactile Sense

"For people who experience sensory decline in vision and hearing, being in an environment that deprives them tactually can limit their potential for mental and physical activity and even produce symptoms of stimulus deprivation and confusion."¹¹ Touching is a powerful nonverbal means of communication. It relieves stress, encourages relaxation, is a sign of acceptance and a vital means for sexual stimulation.

I am reminded of numerous discussions concerning negative staff response toward masturbation among elderly people in residential settings. Certainly respect for the privacy of the elderly is essential. Residents should not be in the vulnerable position of having others barge in on them unannounced.

In Koncelik's book, "The Open Nursing Home," he tells about a facility that offers a room at the end of the corridor, available upon reservation, for those who wish added privacy during sexual intimacy.¹² This type of planning obviously defeats its purpose, is unresponsive to the notion of spontaneity, and borders on being dehumanizing. Butler reminds us that sexual fulfillment is perfectly normal and healthy, and can go on until the end of life. Therefore, attitudes concerning it on behalf of the caregiver and the resident must be positive, and in concert with careful environmental planning.

Hiatt maintains that an issue prevailing in later life is not the loss of touch but instead, the loss of one's touch partner.⁷ In this instance physical contact with objects and other people becomes increasingly important. Without them self-touch-

ing becomes more apparent.¹¹ "A familiar table, dresser or couch may be known more by feel than by sight. Rugs and wall hangings can add texture to an environment, as can furniture and clothing. Furthermore, the presence of personal possessions provides a strong source of self-affirmation.¹² A richly varied tactile environment should be possible not only in private, but also in public and institutional settings that attend to long-term-care."⁵ In terms of personal interactions, physical distance narrows, body language may take on tactile qualities and the personal space of others is more likely to be penetrated.

Although the tactile system is well preserved in later life, the elderly are the least touched in our society.⁵ Children make contact with elderly grandparents while adults tend to withdraw based on their negative attitudes toward aging. Patterns of human contact are reversed for elderly residents in institutional settings whereby the caregivers, as opposed to family members, do the touching and provide the most intimate care.¹¹

There have been discussions in the literature about validating or legitimizing touch (ie, manicures, hair care, shaving, and using lotions). Experienced clinicians have suggested that some forms of incontinence may be in fact motivated to validate touch.¹⁴ "Persons who soil are given professionally and socially approved human contact in the process of cleaning the body."¹¹ It has been suggested that grabbing or clutching may also be overt signs of needing attention.¹¹ Although people differ in their need to be touched, the elderly may not have to be so desperate in finding ways to achieve it knowing that it is part of their services program.

Touching for the sake of communication and social interchange in the physician/patient relationship warrants discussion. It is recommended to approach new patients slowly with perhaps a handshake. Allow individuals to direct you to a "comfortable conversational distance," "good side," or "best ear."¹¹ Offering your hand to vision and/or hearing impaired people tells them that they have your undivided attention and that your comments are intended for them. Keep in mind that people with vision and hearing impairments move closer than usual to the person with whom they speak. Sometimes there is a tendency to take a step backward as one moves closer. Leaning toward elderly people or stooping may be interpreted as being superior. The best solution is to be seated and establish eye contact. Patting the person may be perceived as obligatory and too brief to be enjoyed. Of course,

grandstanding affection for the benefit of others is condescending. Staff members in institutional settings are sometimes observed to show off their willingness to be affectionate through such displays.¹¹

Creating a richer tactile environment includes knowledge from the research on temperature. Elderly people respond favorably to mild, warm, and cool stimuli in spite of the fact that they are sensitive to temperature extremes and have difficulty in maintaining a central body temperature.¹¹ Hiatt offers some suggestions for creating environmental variety through the use of temperature: "being placed in warm sunshine on a cool day; using slightly prewarmed blankets or sheets on chilly evenings; offering some ice in beverages on a warm day; and, perhaps being involved in activities that include warm clay, sand, soil, or dough."¹¹

Koncelik underscores the importance of markers to identify place through touch, especially for the visually and hearing impaired.² Handrails with a groove on the backside tell the traveler where they are and how to proceed. Also, the texture on door knobs in an institutional setting tells the resident if entry to an area is safe or permissible. Research concludes that age alone does not account for diminished sensitivity to touch. Biological events are instrumental as in the case of: Parkinson's disease, multiple sclerosis, minor cardiovascular events that go unnoticed, swollen hands due to reduced blood flow, arthritis,⁴ and perhaps others. Even in these circumstances, new possibilities to stimulate tactile responsiveness need to be explored.

Taste and Olfaction

Part of a discussion on the sensory systems of taste and smell requires simultaneous attention because both systems show apparent decline in later life and have some degree of interaction. At all ages, women display a keener sense of taste and smell.⁵ However, ability to accurately identify flavors and odors becomes less acute for both sexes, with increasing age. Two-thirds of our capacity to taste depends upon our capacity to smell.⁴ Therefore, a decline in one's olfactory function further decreases one's appetite and interest in food. This change is considered to be one of the most dramatic responses to sensory loss.⁹

Safety is affected by a decline in these sensory systems. The inability to taste spoiled food and detect smoke presents serious limitations.

By the time people reach the age of 65 years,

about 50 per cent of their taste buds are lost.⁴ However, a decline in the ability to identify flavors is not likely to occur before the late 70s.⁴ Taste receptors that identify sweetness and saltiness are the first to age while the perception of sourness and bitterness are known to function well into later life. Factors that compound taste deficits are "smoking, poor mouth and dental hygiene, decline in salivation (occurs in later life), receding gum lining, poorly fitted dentures, loss of teeth, and nasal congestion."⁴

Elderly people are likely to enjoy foods prepared with spices, herbs, and flavors (ie, garlic, pepper, horseradish, mustard, spearmint, cloves, onion, and cinnamon) to compensate for their loss of taste.⁵ These stimuli add variety to the menu which in turn contributes to better nutrition. Attention to texture and color further enhance the presentation of food and interest in it which becomes increasingly important. Emphasis on these matters is especially needed in institutional settings.

Compared to young adults, elderly people have found it more difficult to identify objects of smell.¹⁵ Reasons for this sensory decline is not exactly known. Some say it is due to the atrophy of olfactory nerves⁴ while others explain that receptors to the sense of smell may be blocked off by inflammation, nasal disease, or polyps.⁵ Smokers and those in occupational settings with airborne toxic substances lose sensitivity to odors earlier than most people. Ability to associate certain areas in one's living arrangement with characteristic odors may cease to exist (ie, food/kitchen; deodorant/bathroom). Not being able to detect body odors is embarrassing and may be the reason for social isolation. Vulnerability to unsafe situations may prevail as in the case of not being able to smell the additive put into natural cooking gas. As a result of technological advances, safety for the sensory impaired can be enhanced by smoke alarms with auditory and visual cueing and devices to signal a gas leak.⁵

Summary

There is an unprecedented increase in elderly people who are 85 years of age and older. At this point in life multiple sensory deficits become significant thereby limiting their means for gathering information and social interaction. Without sensory function the world becomes inaccessible. Therefore, it is extremely important to maximize the quality of life among the elderly through environmental means. This will offset the perception that most elderly are cognitively impaired

when in fact attention to their sensory loss through adaptive environmental design can maximize well-being. Total wellness is dependent upon it.

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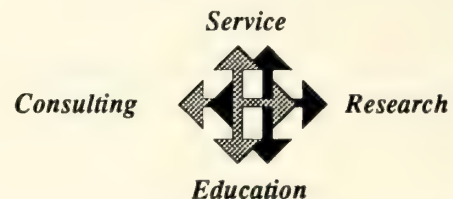
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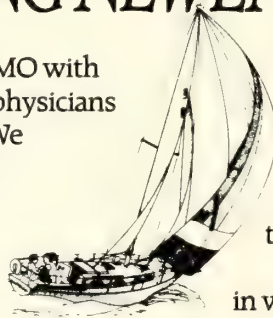
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BRIEF SUMMARY

CONTRAINDICATIONS

There are no known contraindications to the use of sucralfate

PRECAUTIONS

Duodenal ulcer is a chronic, recurrent disease. While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration

Drug Interactions: Animal studies have shown that simultaneous administration of CARAFATE (sucralfate) with tetracycline, phenytoin, digoxin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents. The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. This interaction appears to be nonsystemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The clinical significance of these animal studies is yet to be defined. However, because of the potential of CARAFATE to alter the absorption of some drugs from the gastrointestinal tract, the separate administration of CARAFATE from that of other agents should be considered when alterations in bioavailability are felt to be critical for concomitantly administered drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity. A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment. Mutagenicity studies were not conducted

Pregnancy: Teratogenic effects. Pregnancy Category B. Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug. In studies involving over 2,500 patients treated with sucralfate, adverse effects were reported in 121 (4.7%).

Constipation was the most frequent complaint (2.2%). Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo.

OVERDOSAGE

There is no experience in humans with overdosage. Acute oral toxicity studies in animals, however, using doses up to 12 gm/kg body weight, could not find a lethal dose. Risks associated with overdosage should, therefore, be minimal.

DOSAGE AND ADMINISTRATION

The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach.

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate.

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination.

HOW SUPPLIED

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Reference:

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Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon[®] is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

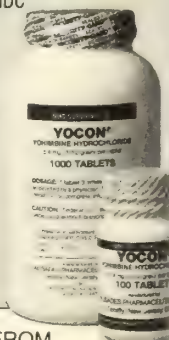
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon[®] 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

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Ectopic Bone in Multinodular Goiter

George N. Tzanakakis, MD
Chrisoula D. Scopa, MD
Michael P. Vezzeridis, MD
Apostolos Vagenakis, MD

Although ectopic bone formation in the thyroid has been described in association with neoplasms such as teratomas^{5, 6} and sarcomas,^{3, 4} the presence of ectopic bone in benign conditions of the thyroid is a very rare phenomenon. We describe here a case of ectopic bone which was incidentally found in the resected thyroid gland specimen of a patient with a non-suppressible multinodular goiter.

Case Report

A 47-year-old white female presented with diffuse enlargement of the thyroid gland which had remained unchanged for four years. During the

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last four months, while under suppression with thyroid hormone, the patient noticed an increase in size of the thyroid with exacerbation of tracheal compression symptoms in addition to signs and symptoms of hyperthyroidism. A thyroid scan was performed which revealed an uptake of 30 per cent, with patchy distribution throughout the gland. The thyroid hormone treatment was discontinued and the symptoms and signs of hyperthyroidism disappeared. Three months later, a thyrotropin-releasing hormone (9TRH) test was performed which showed no thyroid-stimulating hormone (TSH) increase following TRH administration, thus confirming the diagnosis of a non-suppressible goiter. Needle aspiration was negative for malignancy. A total thyroidectomy was performed.

Gross examination disclosed a thyroid gland measuring 8 × 7.5 × 4 cm and weighing 104 gm. Cut section showed heterogeneous multinodularity with some of the colloid-distended follicles appearing hemorrhagic. In addition, focally dense areas were observed. Located in the center of the right lobe a stony hard, pale gray region measuring 1.5 × 0.8 × 0.5 cm was recognized. Microscopic examination revealed multinodular goiter with focal areas of fetal adenoma, and well developed bone tissue (Fig. 1, 2).

Discussion

In man ectopic bone production is a rare phenomenon. Small amounts of ectopic bone are occasionally seen during routine autopsies in the walls of arteries of elderly people, in old oper-

Fig 1. Well developed bone tissue into the thyroid parenchyma (H&E, $\times 25$).

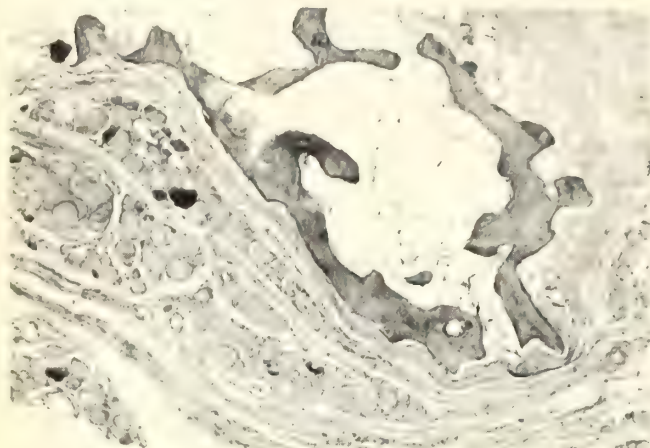
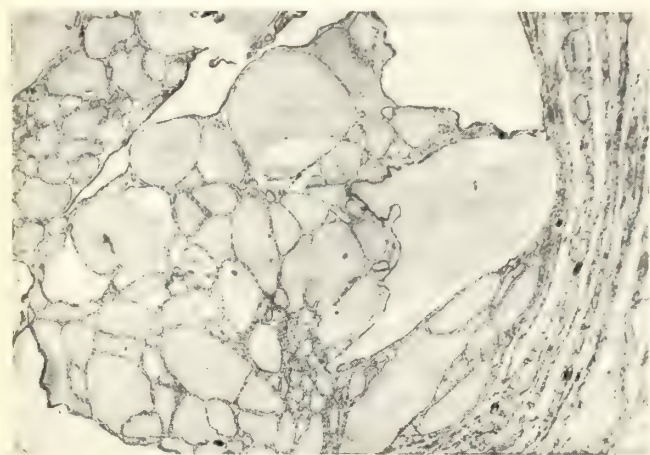


Fig 2. Focus of colloid goiter (H&E, $\times 25$).



ation scars, and in kidneys that have been the site of a chronic, relentless disease process.² Bone has been described along with cartilage and a variety of other tissues in sarcomas and teratomatous tumors.³⁻⁶

Experimental attempts aimed at ectopic bone production had limited success.⁷ Urist and co-workers presented evidence indicating that Bone Morphogenic Protein (BMP), a noncollagenous protein found in bone matrix, is responsible for the inductive effect.¹¹ Experiments utilizing 400-1000 μm sized particles of bone matrix gelatin (BMG) in multiple walled diffusion chambers composed of cellulose resulted in the production of bone on the external surface, due to diffusion of BMP. β -Mercaptoethanol or dithiothreitol reduction extinguishes the capacity of BMG to produce new bone following implantation in a muscle pouch.¹⁰ BMP has not been completely chemically characterized but is known to be al-

kali-sensitive, trypsin-labile,^{8,9} and rich in glycine, aspartic acid, alanine, phenylalanine and tyrosine.¹¹

Ectopic cartilage formation occasionally appears in association with ectopic osteogenesis. This is not surprising since cells destined to produce bone must pass through an osteogenic cell stage, at which time they could differentiate either into bone or cartilage. Ectopic cartilage has been described in multinodular goiter of the thyroid.¹ The histogenetic mechanism of ectopic bone production in a specific microenvironment remains obscure.

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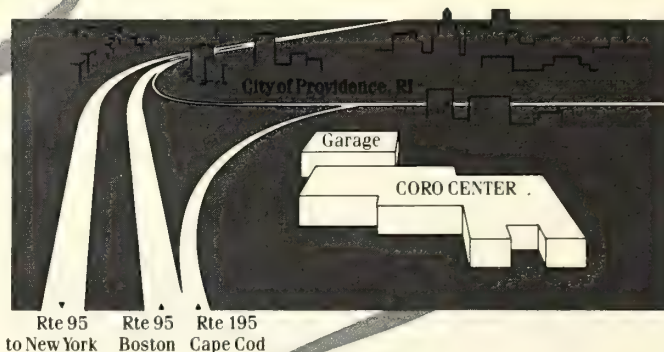


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Delayed Spontaneous Splenic Rupture in Sarcoidosis

Maurice M. Albala, MD
Murat Anamur, MD
John R. Bernardo, MD

Spontaneous splenic rupture is uncommon but has been reported in a variety of disorders associated with an enlarged spleen such as infectious mononucleosis, various hematologic disorders, malignant lesions, inflammatory conditions and collagen vascular disorders.¹⁻⁹ Sarcoidosis involves the spleen with relative frequency.¹⁰⁻¹³ Few reports of spontaneous splenic rupture, however, have been published in association with this condition.^{12, 14, 15} We report one patient with documented disseminated sarcoidosis who developed spontaneous splenic rupture following surgery for an abdominal hernia. At splenectomy, it was found that the spleen was extensively involved with sarcoid granulomata. There were multiple rupture sites associated with areas of necrosis felt to be pathologically related to the sarcoid granulomatous lesions.

Case Report

A 57-year-old female was admitted to the hospital on 6/30/88 for repair of a ventral incisional

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hernia of four years duration. A diagnosis of sarcoidosis was made eight years previously and since that time she had been on low dose steroid therapy. She had a partial gastrectomy for peptic ulcer disease thirteen years ago.

Physical examination revealed a mildly obese female in no distress. Head, Ear, Nose and Throat (HENT) examination showed no abnormalities. No adenopathy was noted. Abdominal examination was normal except for a reducible upper abdominal hernia. The spleen tip was palpable on deep inspiration. WBC was 5,500/cu mm, differential was normal, hematocrit 42.6 per cent and hemoglobin 13.4 per cent. Platelets were normal. Urinalysis was normal. Electrocardiogram was normal. CMV and EBV titers were normal.

Surgical repair of the hernia was performed with limited intra-abdominal exploration because of the presence of adhesions. Approximately ten hours after surgery the patient became diaphoretic and lethargic. Blood pressure was unobtainable. During the hypotensive episode, blood counts showed a sharp drop in the hemoglobin from 13 gms per cent to 6.8 gms per cent. Hematocrit dropped to 25 per cent. Platelet count and WBC count were unchanged. The patient became hemodynamically stable following blood transfusions and fluid replacement.

Forty-eight hours after this episode, the patient experienced a similar episode characterized by hypotension, unresponsiveness, diaphoresis, tachycardia, nausea, left upper quadrant pain, vomiting and dizziness. She was given a fluid challenge with good hemodynamic response. Work-up for myocardial infarction, pulmonary embolism and sepsis was negative. A CT scan of abdomen showed focal defects in the spleen felt

to be consistent with splenic infarcts. In addition, there was evidence of free fluid in the abdominal cavity.

At surgery, a splenic rupture with intraabdominal bleeding was confirmed. Following splenectomy the patient recovered uneventfully.

At laparotomy a 550 gm spleen was removed. There were several linear tears of the capsule, the largest of which measured 13 cm and was partially stripped away from the underlying parenchyma. There were multiple subcapsular and parenchymal hematomas as well as an irregular $3 \times 1.5 \times 1.3$ cm rubbery indurated focus adjacent to the capsule. There was a 0.6 cm ovoid, yellow calcified nodule adjacent to the indurated focus previously mentioned. Microscopically, diffuse non-caseating granulomata consistent with sarcoidosis were present. There were discrete capsular ruptures with underlying hemorrhage, slight necrosis and multiple granulomata. There was no evidence of vasculitis. Stains for acid fast and fungal organisms were negative.

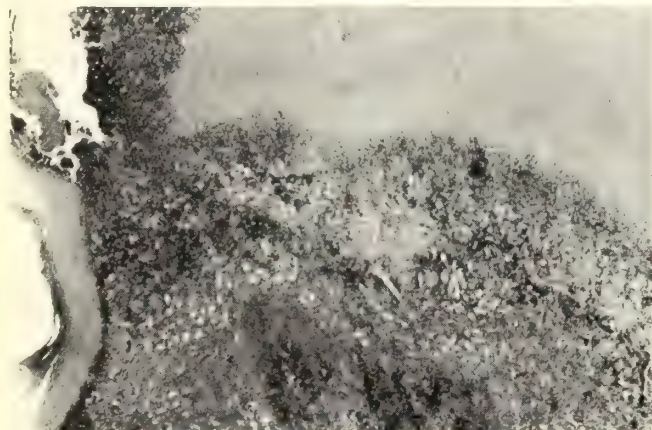
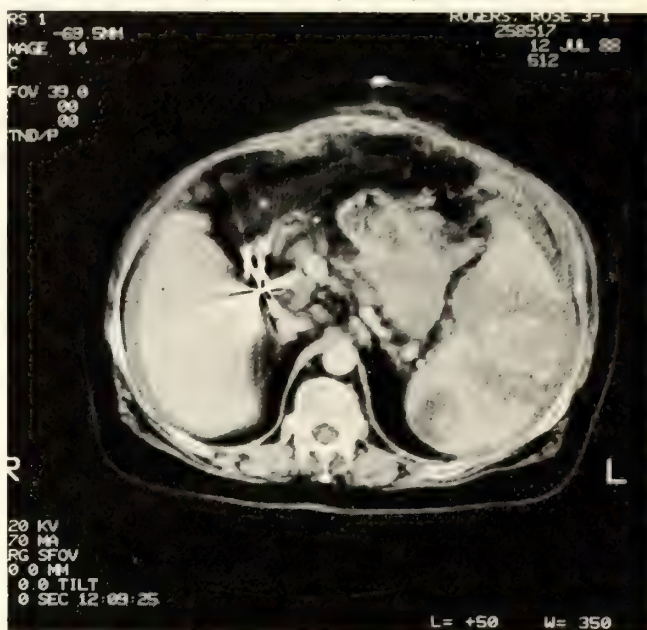


Fig 1. Spleen: Low-power photograph of rupture site with associated granulomata and necrosis.

Discussion

A number of infections have been associated with non-traumatic spontaneous splenic rupture including infectious mononucleosis,^{2,6} infective endocarditis,¹⁶ hepatitis A,¹⁷ chicken pox,¹⁸ malaria,¹⁹ aspergillus²⁰ and influenza.²¹ Less frequently spontaneous splenic rupture is the result of splenic infiltration by leukemia,^{3, 7, 22} lymphoma²³ or primary hemangiosarcoma.⁴ In disorders such as systemic amyloidosis and collagen vascular disorders, splenic rupture has been thought to result from subcapsular hemorrhage due to vascular involvement within the spleen.^{1, 5, 24} Sarcoidosis involves the spleen with relative frequency¹⁰ although marked splenic en-

Fig 2. Contrast enhanced axial CT image of abdomen: Low density intraparenchymal splenic hematoma with associated perisplenic and perihepatic fluid.



largement is rare. Splenic rupture commonly has an acute onset characterized by sudden hypotension, a sharp decline in the hemoglobin concentration and frequently abdominal or left upper quadrant tenderness. Diagnosis of this complication may, however, be quite difficult. Plane radiography yields little information. Ultrasonography has been useful and is commonly employed as a primary method of examination; however, the pleural angle and the ribs may impair visualization of the spleen. Abnormal CT findings are described and in one series abnormalities were observed in all cases in which splenic rupture was confirmed at surgery.²⁴⁻²⁸ The findings included irregularity of splenic parenchyma with hypodense or hyperdense areas which are not enhanced by contrast material. In addition, subcapsular fluid belt and free fluid in the abdominal cavity are common features. These findings should be recognized in patients with enlarged spleen who develop abdominal or left upper quadrant tenderness and a decline in the hemoglobin concentration. A number of mechanisms have been considered to cause splenic rupture in addition to trauma. These include splenic infarction, vascular fragility, associated coagulopathy and mechanical distention due to infiltration or vascular congestion of the spleen. In our patient no clear cut mechanism for the splenic rupture could be invoked. In some instances, sarcoidosis is associated with a granulomatous

vasculitis²⁹ which could lead to parenchymal hemorrhage and subcapsular hematomas with subsequent rupture. However, extensive and meticulous examination of the spleen failed to disclose any evidence of sarcoid granulomatous vasculitis. Although this complication is extremely rare, it is important to be aware that spontaneous splenic rupture may occur in a patient with splenic sarcoidosis so that appropriate treatment be initiated promptly.

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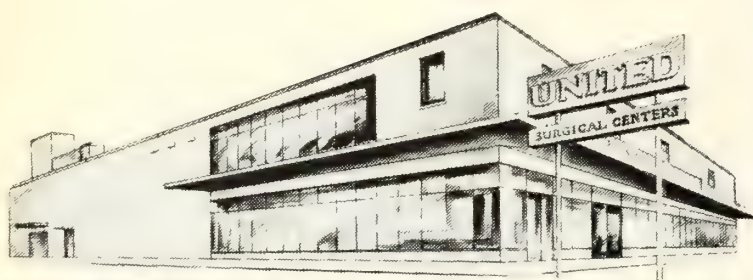
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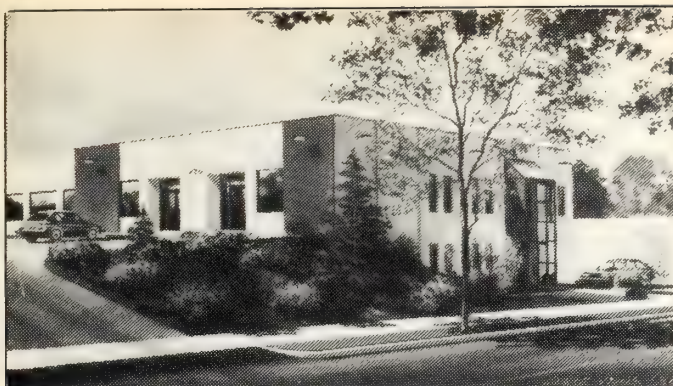
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1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.

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CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

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Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics, see **WARNINGS**.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS**, **WARNINGS**, and **OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS**); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 mEq/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.

3. Correction of acidosis, if present, with intravenous sodium bicarbonate.

4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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Health Care Needs of Homeless and Runaway Youths

AMA Report of the Council on Scientific Affairs

Large number of homeless and runaway adolescents roam the streets of this country, and they can be found in any major city. However, little is known about them, their needs, or their experiences. In fact, the issues surrounding homeless adolescents generally are either ignored or altogether unknown, and, when acknowledged, are most often discussed in terms of homeless families with children, not as independent youths with no homes to which they can return. Much of what is documented about such youths can be found in movies such as *Streetwise* and *Pixot*, both of which are available in video form, or in newspapers and magazines such as *Parade*.¹

The Homeless Adolescent Population

Like estimates of the homeless population in this country,^{2,3} estimates of the number of homeless and runaway youths vary widely. Most of the work in this area has focused on runaways; almost none has examined other homeless adolescents. Using data collected in a probability sample of US households, the number of runaways in this country has been estimated to be between 519,000 and 635,000 annually.⁴ Others estimated the number of runaways to be at least one million annually and perhaps in excess of two million.⁵ Most runaways return home within a week, but substantial numbers stay away longer. One in 20 is estimated to be gone for more than a year.⁶

Corresponding figures for homeless youths are rare. Robertson indicates that there are one million adolescents living on the streets, most of whom do not receive any help from any service agency.⁷ Shaffer and Caton estimate that about one-half of one per cent of New York City's teens between the ages of 12 and 17 use a shelter annually.⁸ If applicable to the entire country, this means that more than 100,000 adolescents in this age group sleep overnight in a shelter in a one-year period. However, most authorities agree that

adolescents are relatively unlikely to use shelters, preferring instead to stay on the streets or with friends and relatives.

The extent to which the populations of homeless adolescents and runaways overlap is unknown, partly because there are no commonly agreed upon definitions of these terms. Runaways are most often thought of as having voluntarily left their homes, choosing to live apart from their families. Homeless adolescents would probably be regarded as those who are involuntarily without shelter.⁹

These distinctions, however, are at best artificial. At worst, they contribute to the lack of understanding surrounding issues of teen homelessness. Adolescents are more likely to consider themselves homeless than they are to regard themselves runaways. For example, among 118 runaways (legally defined) in New York shelters, 56 per cent considered themselves either homeless or both runaway and homeless,^{8,9} that is, they have no home to which they feel they are able or willing to return. Furthermore, the likelihood of defining oneself as homeless increases with age,⁹ although this is influenced to some extent by the fact that, by most legal definitions, one's status as a runaway ends at age 18.

A number of investigators report that large numbers of adolescents are the victims of abuse at the hands of their parents or guardians, and many leave home for this reason.⁸⁻¹⁴ Other homeless youths have been rejected by their families. Gullotta, for example, reports that nearly one-quarter of the youths in a shelter for runaways were forced out of their homes by their parents, and nearly one-half were teens who had been unable to find satisfactory arrangements through a state or local social service agency.¹⁰ Under such circumstances, it can hardly be surprising that many homeless adolescents consider themselves homeless and not runaways.

Health Care Needs

Like other people, homeless adolescents occasionally need medical treatment. However, issues of money, permission, and confidentiality frequently conflict with a youth's need for treatment. As a result, medical care is often unavailable, and delays in seeking treatment are common. The hazy legal status of minors also precludes prompt and full treatment.⁶ Furthermore, guidelines for the treatment of such youths are virtually nonexistent, and this further complicates efforts to provide care. To date, we have found only one shelter that has assembled a protocol for the treatment of the complaints that homeless and runaway youths are likely to present, and that protocol is used only in the medical van operated by the shelter.¹⁵

The health issues surrounding homeless youths are not unlike the health issues facing the homeless population in general. At the same time, adolescents tend to be somewhat more healthy by virtue of their age and the fact that the average time they have been on the streets is less than it is for homeless adults. The health problems faced by homeless adolescents can be grouped into six areas: nutrition, substance abuse, psychiatric problems, physical complaints (especially those related to exposure and hygiene), sex-related medical concerns, and problems associated with victimization and abuse.

Nutrition: Just as it is for the homeless population in general, the supply of food is often inadequate for homeless adolescents. Nutritional deficiencies are common in the homeless population,¹⁶ and large numbers of runaways have difficulty meeting this basic need.¹⁷ Clinics that serve runaway and homeless adolescents frequently note the inadequate nutrition of their clients.^{18, 19} This situation also has frightening implications for the health and well-being of children born to homeless adolescent females, among whom pregnancy is fairly common.

Substance Abuse: Compounding problems caused by inadequate nutrition are high rates of alcohol and drug abuse among these youths. Large numbers of runaways reportedly drink regularly, and up to one-half have diagnosable alcohol problems.⁶ The abuse of other drugs is also common, especially in the central parts of major cities where homeless youths are likely to congregate. For example, in a study in New York City, 70 per cent of the runaways admitted to using illegal drugs, and some admitted to being addicted. Most substance abuse programs do not

have adolescents in their programs, and the majority in fact, exclude adolescents.

Mental Health: Closely related to the problems of substance abuse are high rates of psychiatric disturbances among homeless youths. Most research on the homeless mentally ill has focused on the effects of deinstitutionalization in adults, but homeless adolescents are also afflicted by mental health problems. These problems affect large members of adolescents in the general population,¹³ and, given the difficulties of life on the street, it is likely that relatively more homeless youths suffer from these problems.

According to researchers, the most common mental health problems in homeless adolescents are depression and self-destructive behavior, including suicide.^{8, 9} Antisocial behavior is also commonly reported,⁸ although it is unclear whether runaways are more likely to engage in such behavior or whether those who commit antisocial acts are more likely to run away. A number of researchers argue that running away is a coping mechanism for troubled adolescents.^{17, 20} If correct, it seems likely that runaways are coping with their prior behavioral problems by running away and that later antisocial acts are a continuation of previously established behavioral patterns.

Physical Health: Physical health problems are also common in this population. Living on the streets not only subjects these youths to otherwise avoidable stressors such as the weather, but it also poses difficulties for routine tasks associated with one's personal hygiene. Exposure to the elements, the lack of sleeping quarters, and the absence of a clean domicile all contribute to physical ailments.

The most commonly reported ailments in this group are general malaise and musculoskeletal, gastrointestinal, and genitourinary problems.^{6, 18} Injuries such as broken bones are not infrequent. Among homeless children under 16 who were seen by medical providers as part of the Robert Wood Johnson Foundation/Pew Memorial Trust Health Care for the Homeless program, the most common complaints were upper respiratory infections, minor skin ailments, and gastrointestinal problems.²¹ Unfortunately, in the data from this program, older adolescents are included in a category that encompasses those up to age 29, so information on adolescents is not available.

Sexual Health: Included in genitourinary disorders are both pregnancy and sexually transmitted diseases. Runaway and homeless youths are without doubt sexually active, possibly more

so than other adolescents. Data from a decade ago suggest that, on average, runaway girls experience intercourse two to four years earlier than teenaged girls living at home.²² Moreover, large numbers of adolescent homeless girls become pregnant. Shaffer and Caton found that one-third of the female runaways they interviewed either were or had been pregnant at least once.⁸ In the Health Care for the Homeless program's first year, nearly one-quarter of the females aged 16 to 19 were pregnant on their first visit to a physician or became pregnant during the year; the figure for those who had ever been pregnant would be even larger. Of course, figures for those ever pregnant are inflated somewhat by the fact that some girls run away or are thrown out of their homes after they become pregnant. Contraceptive use among such youths is uncommon.⁸

Sexually transmitted diseases are common in both boys and girls. Data from runaways held in Los Angeles detention facilities indicate that about one-third of the girls have some venereal disease at the time of their detention,⁶ but this figure may be high since other researchers have reported rates that are closer to the rate for the general population, about 1.5 per cent.^{8, 21}

Among the sexually transmitted diseases, there is special concern about AIDS. More than 12,000 cases of AIDS have been reported in people aged 20 to 29, and the virus is believed to have an incubation period of three to five years.²³ If correct, a substantial number of adolescents must be infected with the virus, and, given their level of sexual activity, homeless adolescents represent a high-risk group. (Data presented recently at the Fourth International Conference on AIDS in Stockholm suggest that the incubation period of the virus may be as much as eight years in which case an even larger number of persons may have become infected with the virus during adolescence.) Furthermore, a significant number of homeless youths report having engaged in homosexual behaviors, which further increases their risk of AIDS.^{6, 24}

Victimization: Another factor related to the level of sexually transmitted diseases among homeless adolescents is the degree to which they are victimized by others. Nearly two-thirds of the runaway and homeless youths studied by Kufeldt and Nimmo had been approached and asked to engage in some illegal activity.¹⁷ (The authors did not collect data on the level of participation in such behavior because of concerns about confidentiality.) Unfortunately, their lack of marketable skills and their status as minors leave home-

less youths with few legitimate alternatives to illegal activities. Participation in these activities, however, subjects them to a variety of risk, including disease and both physical and psychological trauma.

Large numbers of homeless adolescents are involved in illegal drug trade, prostitution, and pornography, and many were subjected to sexual or physical abuse before they became homeless.¹⁴ Some 900,000 youths, two-thirds of whom are female, are involved in prostitution; their average age is 15.⁶ Nearly four-fifths of adolescent female prostitutes may be runaways, and a sizable number of young male prostitutes are runaways as well.⁶

The role that prior victimization plays in creating runaway youths who consider themselves homeless cannot be overstated. Teenage girls have frequently been sexually abused by family members in their homes,¹⁴ and physical abuse is also common. Indeed, the level of physical abuse in runaways has been reported to be as severe as among adolescents under the care of child protective services or seen in hospital child abuse clinics.^{25, 26}

Providing Health Care

Providing treatment for the health problems of homeless adolescents is complicated by the very behaviors associated with homelessness. Most of these youths believe that without the money to pay for treatment, medical care is unavailable to them. Additionally, most homeless adolescents are untrusting of authority figures such as physicians, delay seeking medical attention until problems become so severe that help-seeking can no longer be postponed, and neglect to return for follow-up care.^{6, 19}

While little can be done about the latter two factors, some authorities have suggested that health care providers could improve their interaction with youths and thereby improve compliance and encourage return visits. In general, providers are advised to treat such patients in as nonjudgmental and nonthreatening a way as possible and to encourage the patient to fully discuss his or her health complaint and the reasons for his or her homelessness. Insofar as possible, maximum treatment should be given at the initial visit since the adolescent's return cannot be expected with any certainty.^{6, 27} In addition, some advocates for runaway youths believe that health care providers should form linkages with programs that serve youths so that they can become knowledgeable about the particular needs

of such youths and aware of resources in their locales.

Legal Considerations: Notwithstanding the efforts of individual providers, however, significant barriers to treatment remain because of the questionable legal status of homeless adolescents. Board of Trustees Report LL (A-86) noted that adolescents who are outside the guardianship of a family are often barred from health care by the inability to give legal consent as well as by the lack of documentation that would enable them to qualify for public assistance programs.

At the same time, all states allow some care to be provided to minors without parental consent under certain, often specialized, circumstances. For example, under Illinois' Good Samaritan Act a physician can treat a minor if three conditions are met: the condition is life threatening, the physician has had no prior contact with the patient, and there is no charge for the services provided.²⁸ Nearly all states allow minors to be treated for venereal disease without parental consent, and both federal and state laws have been enacted to permit children to receive treatment for such problems as drug and alcohol abuse without parental consent.²⁹

Similarly, providing counseling services to a minor without the consent of his or her parents is more than likely permissible. Liability would probably be limited to those cases in which the care is so outrageous as to be "beyond any tolerable boundaries of human conduct."²⁹ In fact, in the case of counseling by a mental health professional, there are no reported cases of liability for providing care to a minor without parental consent.²⁹

Several states also have passed laws defining emancipated minors — a status that probably applies to many homeless adolescents. These laws permit adolescents to consent to medical treatment if the physician provides full disclosure and ensures the patient's understanding of the procedure and its consequences. In general, an emancipated minor is living apart from his or her parents, with or without their consent and, in addition, is self-supporting and managing his or her own financial affairs.³⁰ Where specific legislation has not been enacted, arguments for emancipated minors can be found in common law.²⁹ Youths meeting the definition of an emancipated minor may be able to consent to treatment. According to Croxton, there are no reported cases imposing liability on a physician or hospital for failing to obtain parental consent where the minor was at least 15 years old.²⁹

Recommendations

Experts generally agree that homelessness among adolescents is increasing. However, data on the extent of the problem of homelessness in adolescents is sorely lacking. For example, the number of such youths is unknown, knowledge of their health care needs is based more on speculation and anecdotal information than on hard data, and differences between the adult and adolescent homeless populations are glossed over. Virtually nothing is known about the needs of subgroups within the adolescent homeless population or about what happens to these youths as they age. Undoubtedly, some of these children die on the streets.

In addition, few specifics are really known about the health care needs of these youths. Medical care for homeless adolescents is generally considered to be inadequate for a variety of reasons, including a shortage of facilities, the behavior of the adolescents themselves, the ability of providers to deal with such youths, and legal complications of providing treatment, but again, there is a dearth of scientific data on these issues. For those youths who do come into contact with service providers or agencies, there is little information on treating their needs. Guidelines for the treatment of such youths are virtually nonexistent, and those guidelines that do exist are not widely known. These issues merit close study.

In view of these conditions, the Council on Scientific Affairs recommends that the American Medical Association:

1. Urge that a national study that would provide accurate, timely and reliable data on homeless adolescents be funded by an appropriate government agency;
2. Consider conducting a pilot study of the health care needs of homeless youths in a major city to provide physicians with solid, baseline data on this issue;
3. Explore the feasibility of establishing a protocol to be used in the evaluation and treatment of homeless youth;
4. Disseminate information on the lack of treatment facilities and health care providers for treating homeless youths;
5. Encourage state medical societies to determine the extent of treatment possible under state laws, to inform physicians of the laws and regulations affecting the treatment of minors, especially those who are homeless, and to form linkages with statewide youth advo-

cacy groups to develop protocols for the treatment of troubled youths;

6. Encourage local medical societies to develop and publicize lists of local and regional resources that can assist homeless adolescents, to provide this information to local physicians, and to establish links with providers of youth services in order to improve knowledge of the needs and limitations of the youths themselves and physicians who provide care.

The above proposals from Report D of the Council on Scientific Affairs were adopted by the AMA House of Delegates at its Interim Meeting held in Dallas, Texas, December 4-7, 1988.

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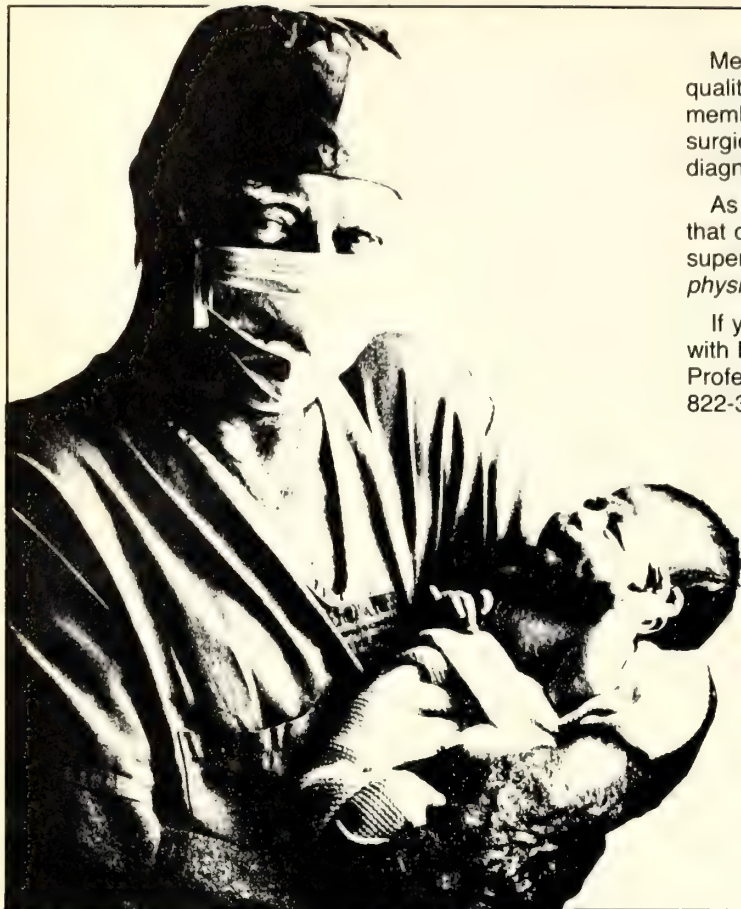
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PERIPATETICS

Dr Albert S. Most, Physician-in-Chief of the Division of Cardiology, has been named Chief of Medicine at Rhode Island Hospital. He will direct the clinical, academic, research and administrative activities of the Department of Medicine and its eleven medical divisions.

• • •

At the first National Cholesterol Conference sponsored by the National Institute of Health's National Cholesterol Education Program Coordinating Committee, **Dr Richard A. Carleton**, Physician-in-Chief at Memorial Hospital and principal investigator of the Pawtucket Heart Health Program, addressed a plenary session on cholesterol screening. **Dr Carleton** is chairman of the population-based panel for the National Cholesterol Education Program, which will help set national policy regarding cholesterol screening and control in the general population.

• • •

Women and Infants Hospital of Rhode Island has named **Dr Patrick J. Sweeney** as Director of the Division of Ambulatory Care of the Department of Obstetrics and Gynecology. **Dr Sweeney** will assume this position on July 1, 1989.

• • •

The High Blood Pressure Committee of the American Heart Association, Rhode Island Affiliate, has named **Dr Paul D. Levinson**, a member of the endocrinology division at Memorial Hospital of Rhode Island, as its chairman.

• • •

Dr Don B. Singer, Chief of Pathology and Laboratory Medicine at Women and Infants Hospital of Rhode Island, has been elected to a one year post as president of the Society for Pediatric Pathologists.

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Treatment of physicians for alcohol addiction shows a favorable outcome in 83 per cent of cases, and treatment of physicians for drug addiction has a 95 per cent success rate. More than 70 per cent of the physicians entering treatment return to the active practice of medicine.

The Rhode Island Medical Society Committee on Impaired Physicians, chaired by Dr Herbert Rakatansky, meets monthly. It is a standing committee of the Society charged with "helping physicians whose professional judgments and capabilities are impaired by their difficulties with chemical dependency or other illnesses."

The Committee handles inquiries in *complete confidence*. If you know of a physician who needs an advocate and support in obtaining necessary treatment, please call or write Dr Rakatansky c/o The Committee on Impaired Physicians, Rhode Island Medical Society, 106 Francis Street, Providence 02903 (401/331-3207).

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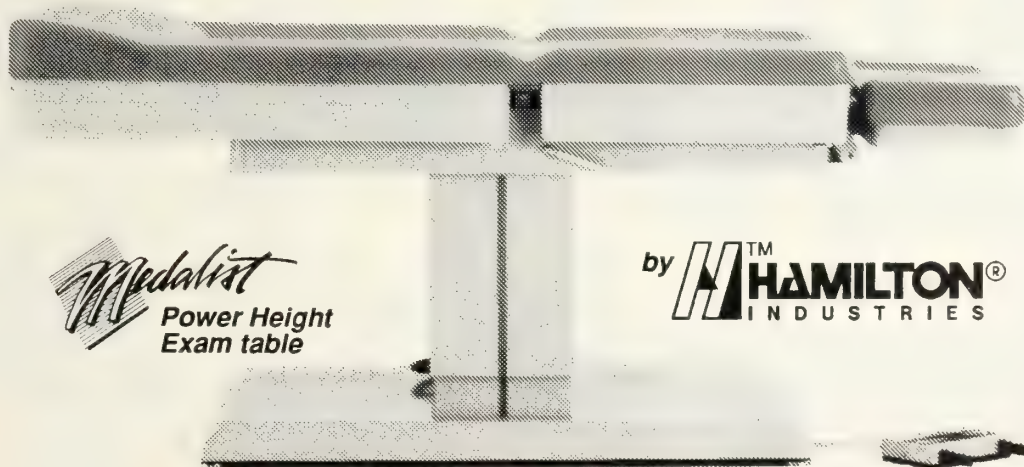
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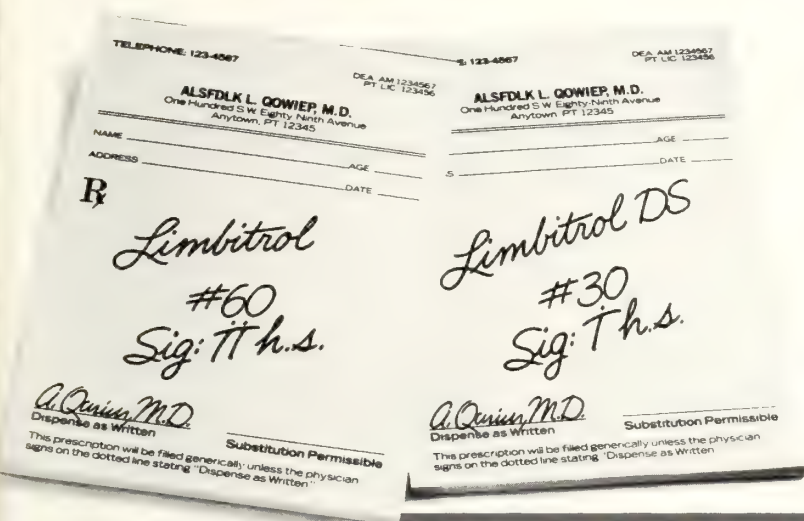
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Warnings: Use with caution in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur when used with anticholinergics. Closely supervise cardiovascular patients. Arrhythmias, sinus tachycardia, prolongation of conduction time, myocardial infarction and stroke reported with tricyclic antidepressants, especially in high doses. Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

Usage in Pregnancy: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations. Consider possibility of pregnancy when instituting therapy.

Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: Use cautiously in patients with a history of seizures, in hyperthyroid patients, those on thyroid medication, patients with impaired renal or hepatic function. Because of suicidal ideation in depressed patients, do not permit easy access to large quantities of drug. Periodic liver function tests and blood counts recommended during prolonged treatment. Amitriptyline may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady-state concentrations of the tricyclic drugs. Use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Should not be taken during the nursing period or by children under 12. In elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.

Adverse Reactions: Most frequent: drowsiness, dry mouth, constipation, blurred vision, dizziness, bloating. Less frequent: vivid dreams, impotence, tremor, confusion, nasal congestion. Rare: granulocytopenia, jaundice, hepatic dysfunction. Others: many symptoms associated with depression including anorexia, fatigue, weakness, restlessness, lethargy.

Adverse reactions not reported with Limbitrol but reported with one or both components or closely related drugs: **Cardiovascular:** Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke. **Psychiatric:** Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania, increased or decreased libido. **Neurologic:** Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns. **Anticholinergic:** Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract. **Allergic:** Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus. **Hematologic:** Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia. **Gastrointestinal:** Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue. **Endocrine:** Testicular swelling, gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion. **Other:** Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Drug Abuse and Dependence: Withdrawal symptoms similar to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of chlordiazepoxide; more severe seen after excessive doses over extended periods; milder after taking continuously at therapeutic levels for several months. Withdrawal symptoms also reported with abrupt amitriptyline discontinuation. Therefore, after extended therapy, avoid abrupt discontinuation and taper dosage. Carefully supervise addiction-prone individuals because of predisposition to habituation and dependence.

Overdosage: Immediately hospitalize patient. Treat symptomatically and supportively. I.V. administration of 1 to 3 mg physostigmine salicylate may reverse symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

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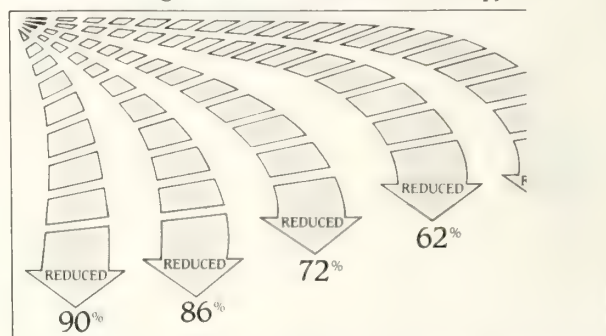
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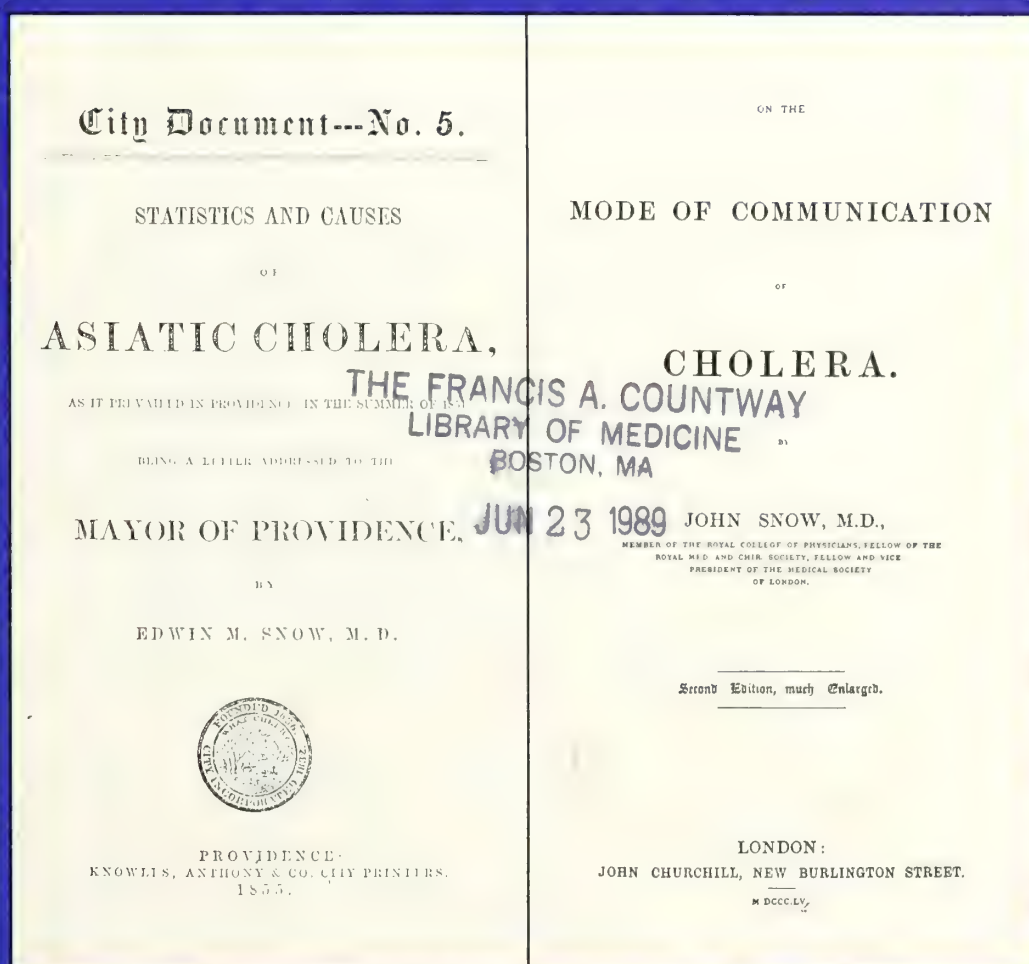
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RHODE ISLAND MEDICAL JOURNAL

June 1989

Volume 72, Number 6



*Developments in
Oral Rehydration Therapy*
(See page 203)



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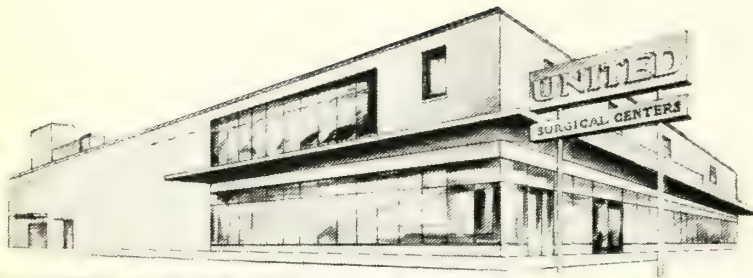


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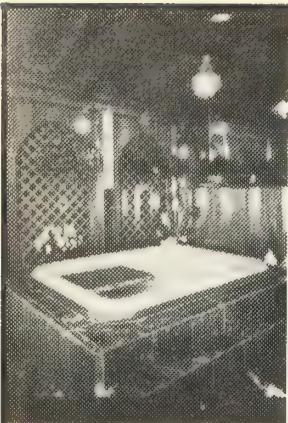
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Cover: *The frontispieces of two seminal articles on the causes and modes of transmission of cholera. Both of these reports were published in 1855, one in London and one in Providence. By coincidence, the authors of each were named Snow, although unrelated to each other. In the current issue of this Journal there is an article by Lee discussing developments in oral rehydration therapy, the therapeutic means by which cholera and other fluid-losing diarrheas are now controlled.*



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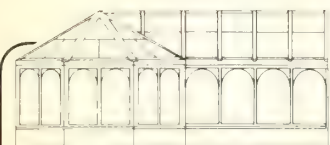
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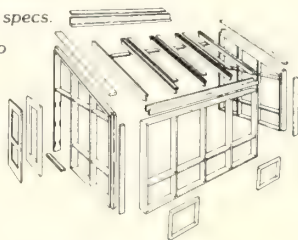
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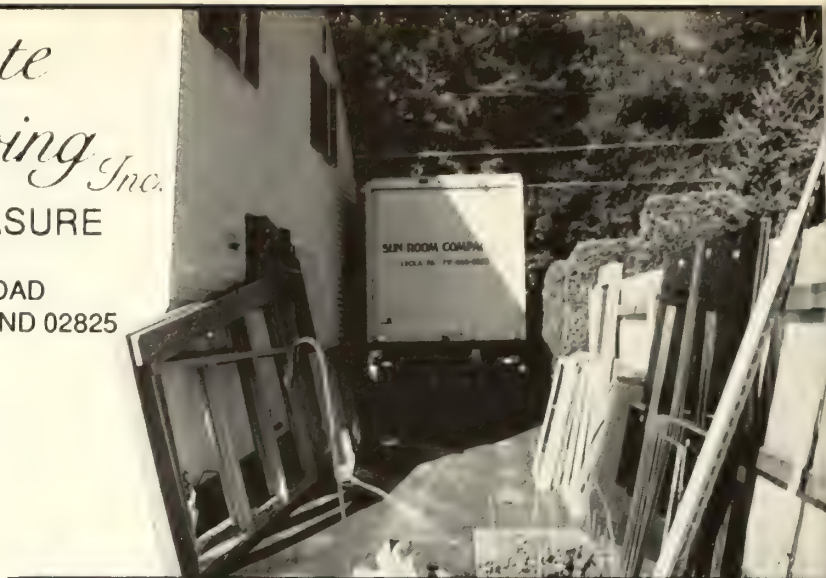
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EDITORIAL

The Mission of the *Journal*

State medical societies have customarily provided their membership with professional and scientific information through the medium of published transactions, periodic newsletters and sponsored journals.

The Rhode Island Medical Society inaugurated its own publishing efforts in 1858, during James Buchanan's presidency, when it distributed the transactions of its stated meetings to its membership. In 1884 when Chester Arthur was president, the Society began a monthly journal called *Rhode Island Medical Science Monthly*. The publication then underwent numerous editorial changes, emerging in 1896 as the *Atlantic Medical Monthly* and in 1899 as the *Providence Medical Journal*.

It was not until 1916 that the Society elected to consolidate all of its publishing efforts into a single monthly enterprise, the *Rhode Island Medical Journal*. The initial issue was distributed in November, 1916 as Woodrow Wilson was completing the final year of his first presidential term.

The *Journal* has since continued its monthly publication, providing scientific observations and professional news to its physician-members and other interested readers.

These 73 years of uninterrupted *Journal* publication have borne witness to immense societal change. The Rhode Island population has more than doubled; the number of physicians and health care institutions within the state has more than tripled; a medical school has been re-established at Brown; and the preparation and skills of the practicing physician in Rhode Island have undergone immense growth. Certainly the successes of scientific medicine have been instrumental in the dramatic increase in median life expectancy during these preceding eight decades.

The availability of printed scientific material to the practicing physicians has grown even more substantially. Where formerly there was but a sparse number of published journals, there now is an expanding flood of scientific publications, many subscription-free, reaching a volume which taxes the capacity of even the most voracious reader. Certainly we are not in want of super-

fluous journals.

In 1916, when the *Journal* was born, the only comprehensive medical library in the state was found in the Society headquarters. Today, Brown and virtually every hospital in the state possess an intramural library of respectable proportions and frequently offer local computer capability for the most sophisticated of literature searches and retrievals.

As our profession has evolved and our access to biomedical information has expanded, the legitimate role of the *Rhode Island Medical Journal* necessarily demands serious reappraisal. Accordingly, the Publications Committee of the Society, chaired by Ed Feller, MD, was convened to determine how the *Journal* can now serve the current needs of the Society and its membership. After much discussion, both the Committee and the Editorial Board of the *Journal* have agreed upon the following statement of mission in answer to this legitimate question: "What singular values and benefits can the *Rhode Island Medical Journal* offer to the physicians of Rhode Island in 1989 and the years beyond?"

The *Journal* identifies the following services which it will strive to provide:

1. A place where the officers and committees of the Rhode Island Medical Society may share their views and concerns and then collectively recommend actions which reflect the best interests of the physicians, health-care professionals, the citizens and institutions of the state.
2. A channel for both Society members and *Journal* editors to express their opinions via letters to the editor and signed editorial statements.
3. A journal for scientific articles written by local physicians so that they may share professional experiences and observations particularly as they uniquely concern the Rhode Island community and its environment.
4. Listings of scholarly lectures, postgraduate courses, continuing medical education exercises and other medical events in the greater Rhode Island community.

5. Epidemiologically oriented articles describing the Rhode Island population and its evolving changes in risk exposures and disease rates. Rhode Island is now immensely enriched by a number of Brown University-associated scientific centers (such as the Pawtucket Heart Health Program headed by Dr R. Carleton, the Center for Alcohol and Addiction Studies headed by Dr D. Lewis, and the Southeastern New England Gerontological Center headed by Dr V. Mor) which undertake scientific inquiries involving major segments of the Rhode Island community. When completed, many of these population-based investigations offer unique educational guidelines to our practicing physicians by providing them with a perspective of certain secular trends and subtle regional forces which are not generally apparent through encounters with either individual patients, or nation-wide statistics.
6. In recent years, the service functions and purposes of the Rhode Island Department of Health have been expanded and diversified. The *Journal* is a natural medium where the numerous public health activities of the Department may be shared periodically with the Rhode Island medical community. These activities currently embrace such essential services as the assembly of vital statistics, the surveillance of various infectious diseases, industrial and ecological hazards, and data gathering on yet other phenomena (such as motor vehicle accidents) which impinge upon the practice of medicine.

The Centers for Disease Control in Atlanta issue a biweekly summary of disease statistics and trends, particularly those which are communicable. The Rhode Island-derived data from CDC may be summarized in the *Journal* at monthly intervals along with the state's vital statistics.

7. The clinical and basic science departments of the Brown University medical school have matured in the last two decades and some have now achieved national stature. Solicited articles from these faculty may offer the *Journal* readers scientific insights of particular import to the southern New England region and its population. The pages of the *Journal* may also be opened for qualified and relevant contributions by the many graduate and medical students now attending Brown University.

There are other Rhode Island institutions

of higher learning with impressive scientific faculties whose scientific interests on such subjects as environmental pollution touch the concerns of practicing physicians. Solicited articles from the faculty of the University of Rhode Island, for example, may give another dimension to the scientific content of the *Journal*.

8. Publication of selected, outstanding hospital-based lectures and conferences, particularly interdisciplinary exercises such as clinical pathological conferences, which may be offered at regular intervals.
9. The state of Rhode Island has a rich and intriguing heritage in medicine and the allied sciences. A periodic synopsis of the medical views and customs of 25, 50, 100 and 200 years ago would provide the reader with an historic perspective and a sense of evolution of the art and science of medicine.
10. As the practice of medicine affirms its capacity to control certain diseases and prolong human life, it will necessarily cogenerate increasing numbers of ethical dilemmas. It becomes important, then, that the pages of the *Journal* be opened to statements which address such moral concerns, contributed by qualified state officials, social scientists, members of the clergy and physicians.
11. Many issues of substantive concern to Rhode Island physicians cannot be explored adequately in isolated articles. Increasingly, then, the *Journal* will edit its contributions so as to assign entire issues to the exposition of single subjects. In the next year, for example, there will be *Journal* issues expressly confined to such diverse subjects as the role of hospice in the care of the terminally ill patient; tropical disease and the Rhode Island community; the floppy baby; and newer aspects in the care of the alcoholic patient.

In summary, then, the *Rhode Island Medical Journal* is a local publication which strives to meet the needs of its members and other health-related professionals through locally-authored scientific and socioeconomic articles as well as current epidemiologic data and ethical issues affecting the practice of medicine.

The editorial board encourages commentary from the readers on this statement of purpose and welcomes specific suggestions for the content of future issues of the *Journal*.

Stanley M. Aronson, MD

For the Publications Committee and Editorial Board

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EDITOR'S MAILBOX



Medical Dichotomy

Some years ago, the *Providence Journal* had a page full of excellent quotes. Two of these which impressed me were:

- (1) "Pride in workmanship has been lost" (by a RI tailor)
- (2) "Education is being strangled by degrees" (an educator)

The second one which correctly implies that a teacher is rated by the number of degrees earned whereas actual teaching ability and experience plays a secondary role. In my opinion this concept can be applied to medicine for I have no-

ticed that academia has placed the "paper writers" and researchers on a pedestal at the expense of the many excellent clinical doctors who have performed a fantastic job in teaching at the bedside and in the operating rooms.

The existence of this dichotomy is responsible for the discordance existing in medical education and needs correction in order to equalize these two phases. Deemphasis by the medical schools and hospitals on academia is necessary and the heavy work load of the clinicians in teaching must be more fully appreciated.

A.V. Migliaccio, MD

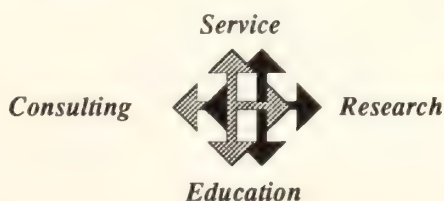
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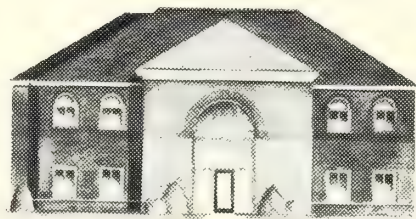


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Starch-based Oral Rehydration Therapy and Its Application

Brent Lee

"The discovery that sodium transport and glucose transport are coupled in the small intestine so that glucose accelerates absorption of solute and water was potentially the most important medical advance this century."¹

How could such a seemingly trivial piece of physiological knowledge impact upon the lives of so many millions? The answer is diarrhea. Deaths, worldwide, due to diarrheal diseases are estimated at anywhere from 3 to 18 million per year.³ Diarrheal dehydration is one of the major causes of death in children five years of age particularly in developing countries.³ In addition, periodic diarrhea accompanied by dehydration and malnutrition are detrimental to the growth and development of those children who do survive.³ But the toll of diarrheal diseases is not limited solely to the countries of the developing world. In the United States for example diarrhea remains a common reason for admitting children to the hospital.⁴ Two other groups with high diarrheal rates are the elderly and the new and growing population of AIDS patients.^{5, 6}

During acute diarrheal illness there is a substantial loss of body fluids and electrolytes resulting in dehydration, the major life threatening consequence of diarrhea. In the past, intravenous therapy was the sole method of replacing these vital fluids and solutes and is still advised

today in the 5-10 per cent of cases where the patient is unable to be rehydrated by other means.^{2, 4} However, the bulk of patients suffering from acute watery diarrhea, regardless of the cause, may be treated with oral rehydration therapy (ORT).² This is a simple process in which the patient is fed a solution of water, sugar and salt as well as other electrolytic solutes (oral rehydration solution [ORS]), in an effort to replace the deficits. ORT was initially proposed in Great Britain in the 1830s, although it wasn't until the 1960s that the importance of sugar was appreciated.⁷

In the 1970s and especially in 1971 during the cholera epidemic in Bangladesh, the efficacy of ORT was conclusively demonstrated.³ In 1978 the World Health Organization (WHO), jointly with UNICEF, launched a global diarrheal diseases control program (CDD) which became fully operational in 1980.⁸ The major effort of this program since its inception has been directed towards achieving the widespread use of ORT for prevention and treatment of dehydration. While various fluids may be used for ORT, the treatment of choice by the CDD has been a universal prepackaged ORS consisting of:

- | | |
|---|--------|
| 1. sodium chloride | 3.5 g |
| 2. trisodium citrate, dihydrate | 2.9 g |
| or | |
| sodium hydrogen carbonate
(sodium bicarbonate) | 2.5 g |
| 3. potassium chloride | 1.5 g |
| 4. glucose | 20.0 g |

which is to be dissolved in one liter of clean drinking water.²

While to date this standard formula has proven itself to be the most efficacious and safe, recent studies have considered alternative formulas which not only would replace the lost fluids due to diarrheal dehydration but would also decrease

Brent Lee is an undergraduate student at Brown University. This paper on oral rehydration therapy in diarrheal disease represents his term paper in a course entitled, The Burden of Disease in Developing Countries. In the Fall of 1989, he will be a first year medical student in the Brown University Program in Liberal Medical Education (MD '93).

vomiting and reduce the severity and duration of diarrhea.⁹

... Diarrheal dehydration is one of the major causes of death in children five years of age particularly in developing countries.

In cases of diarrheal disease the small intestine's excessive secretion of fluids results in hypovolemia and decreased circulation.⁴ The glucose molecule provided by ORS facilitates the transport of sodium across the epithelial cells of the small intestine via a highly specific transport mechanism.¹⁰ The transport of sodium and glucose across the intestinal mucosa also promotes the absorption of isotonic fluid. Thus the aim of this therapy is to counterbalance the enterotoxin-induced fluid secretion by the glucose-facilitated absorption of isotonic fluid.¹¹ The limiting factor of this therapy, however, is the osmotic activity of the intestinal epithelium which is a very "leaky" membrane and tends to equilibrate osmotic gradients rapidly.⁴ The osmolarity of the glucose solution must therefore not greatly exceed the osmolarity of plasma or a resultant "back drag" will occur.¹² Consequently the substitution for glucose in ORS as a source of cotransport molecules by substances with lower osmolarities has been suggested.¹³ Food polymers are naturally occurring sources of such substances. Starch is essentially a large polymer of glucose and may take the form of a number of different cereals such as rice, corn, wheat, potato, sorghum, millet or plantain. These starches are digested by the enzyme amylase into smaller polymers and eventually further broken into glucose molecules at the intestinal brush border by the enzyme maltase.⁴ This digestive process provides a larger number of glucose molecules for sodium transport into the lumen without the osmotic "penalty."⁴

Another advantage of using starch instead of glucose in ORS is the provision of small peptides and amino acids which also facilitate sodium transport via cotransport mechanisms similar to but separate from glucose.⁴ Furthermore the use of cereal-based solutions might enhance the nutritional and caloric intake during the acute phase in diarrhea.⁴ Finally the glucose-based solution serves primarily to replace fluids lost in the watery stool of a patient. Because it does not decrease the volume of stool output and may in fact increase it, the treatment may appear ineffective

to the user who may therefore discontinue its use.⁴ Improper preparation of glucose-based solutions by the addition of too much solute to the standard volume of water would also produce a hypertonic solution with an increase in diarrhea and hypernatremia.⁴ Studies using cooked cereal powder have proven to be equally effective in restoring volume losses and may reduce both the duration of the illness and the volume of fluids lost.¹⁴ But the question remains, what are the practical applications of a starch-based ORS in the world-wide ORT effort?

According to the 1985 WHO/UNICEF joint statement entitled "The Management of Diarrhea and Use of Oral Rehydration Therapy," the WHO will,

"Support and encourage research to find new drugs and vaccines and to develop, if possible, a less costly and even more effective and stable ORS product;²

In the past such improvements have indeed been made in the components and packaging of ORS. The acceptance of trisodium citrate in the ORS formulation in place of sodium bicarbonate is a prime example of this.¹⁵ Not only is this compound more stable when packaged under conditions of heat and humidity but according to some studies may also reduce the amount of diarrhea.¹⁶

... the use of cereal-based solutions might enhance the nutritional and caloric intake during the acute phase in diarrhea.⁴

Additionally the costs of packaging ORS have been reduced through the use of polyethylene packaging materials, where possible.¹⁵ Studies examining the possibility of replacing glucose with precooked cereal powder in ORS are presently being undertaken.⁴ Provided that the results of these studies prove feasible in terms of the cost and perishability of cereal-based solutions, the added benefit of this formulation in reducing the severity and duration of diarrhea may prompt a revision in current CDD programming.

However, prepackaged packets of ORT are only a partial answer to the prevention of morbidity and mortality due to diarrheal dehydration. In the joint WHO/UNICEF statement the program recommendations include a directed effort on the household level to inform and train mothers and other members of the family "1) to recognize diarrhea in infants and children as an

illness requiring early treatment; 2) to prepare and give a home remedy by mouth and 3) to recognize when they should seek additional care, including ORS."² This home therapy is an attempt to *prevent* dehydration while ORS is needed to treat most cases of dehydration, and intravenous therapy is required to treat cases of severe dehydration.² Such household solutions would inevitably vary from region to region depending on such factors as availability and prices of the ingredients, cultural factors, and the presence of accurate measuring devices. But with proper instruction it has been demonstrated that acceptable solutions can be prepared by mothers using common salt and sugar.¹⁷ Given that these home-made ORS's are less than ideal (due to the lack of sodium bicarbonate and potassium chloride, for instance), reasonably accurate measurements are nonetheless possible even in the most impoverished households. Water for example can be measured using one liter carbonated beverage bottles and bottle caps can be used to measure the salt (one level capful) and sugar (seven-eight heaping capfuls).³

Homemade ORS is not only less expensive than WHO ORS but it is also more accessible to mothers in the developing world.³ While this strategy may initially require more of the health workers' time to train mothers in the preparation and administration of ORS, the long term results are evident. It would free the hospital and health center staff for other duties and would provide the opportune occasion for the health workers to communicate other equally important health education messages on diarrhea prevention and nutrition. Ultimately this strategy also involves the parents directly in the health care of their children. In essence it returns the responsibility and "power" to the people.

... with proper instruction it has been demonstrated that acceptable solutions can be prepared by mothers using common salt and sugar.¹⁷

Home preparations of ORS also alleviate logistical problems which arise when prepared packets are in short supply. It is estimated that in order to prevent death by diarrheal dehydration in children under five years of age, about six packets per child are required per year.³ This estimate would total approximately 2400 million packets a year for the world's population of chil-

dren excluding those in the People's Republic of China. The 1986 world supply of packets stands at about 270 million.⁷ Each packet costs approximately eight cents to produce, which seems manageable. However, in a nation such as Egypt which requires, currently, about 60 million packets per year, the annual costs approach five million dollars.³

For these reasons it is logical to investigate the utility of cereal-based solutions. Different countries use different sources of starch, such as wheat, sorghum, potato, maize and rice. Rice alone is eaten by 60 per cent of the world population¹⁸ and thus such starch staples would be more accessible and cheaper for ORS preparation in the developing world than would sucrose or glucose. Extensive studies need still to be undertaken to determine the appropriateness of these preparations. Not only must the clinical efficacies of the various starches be examined and weighed against their costs, feasibility and availability, but regional sociocultural practices must also be evaluated.

Research must press forward in search of other improvements in ORT.

Certainly in the years since the launching of WHO's diarrheal diseases control program (CDD), progress in the reduction of morbidity due to diarrheal disease has been made. Between 1982 and 1985 the number of countries with national diarrheal disease control (CDD) programs doubled, access to ORS increased from 6 per cent to 33 per cent by 1984, and the annual production of ORS rose from 110 million packets in 1983 to 270 million packets in 1985 with the majority being produced in 42 developing countries.¹⁵ The success of the program can in part be attributed to the universal acceptance and promotion of a standard oral rehydration solution. This solution which WHO and UNICEF began to recommend in 1971 was selected because it could be used to treat diarrhea of any cause, including cholera, irrespective of age.² In addition the adoption of a universal solution has simplified the production and distribution of the ORS ingredients as well as the training of health care personnel, thereby increasing availability and assuring safety.² The aim of ORT has been to correct dehydration (the rehydration phase) and to maintain hydration during continuing diarrhea (the maintenance phase). This standard solution has the advantage of safely and effectively accom-

plishing both. Thus the possibility that the introduction of a new starch-based ORS could have a negative impact on the existing prepackaged standard glucose solution must be considered. The use of food polymers will require not only quality control efforts if they are to replace glucose but also will necessarily vary according to dietary preferences and availability.¹⁹

It has also been cautioned that solutions containing rice or other cereal powders whether prepared in packets or in the home, may be confused with weaning foods.¹⁵ Furthermore because they are made from cereals these solutions may discourage feeding during diarrhea.¹⁵ However, such negative consequences of using starch-based ORS remain speculative until field trials explore these operational issues. The current programs which encourage the use and availability of packaged glucose-based ORS along with the programs which foster education at the household level, must therefore continue and be reinforced.

In addition research must press forward in search of other improvements in ORT. Other new and exciting prospects are in their initial stages of research. Proteins or polypeptides (sources of neutral amino acids) and glucose polymers (eg, maltodextrins) are two examples of such improvement efforts.⁴ The application of starch-based oral rehydration solutions is one specific example among many of the complex predicaments which advancing technology creates in translating its findings to the needs of the people in developing nations.

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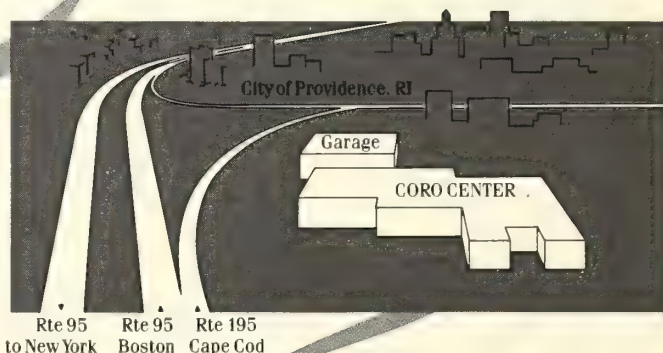
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Rhode Island Hospital Physicians and AIDS

A Survey

Larry K. Brown, MD
Nancy Rowett, APR
Stephen A. Dwight
Vincent J. Barone, PhD

As the prevalence of acquired immune deficiency syndrome (AIDS) increases in our society, more physicians will be faced with the reality of treating HIV-infected patients. In the United States over 86,000 AIDS cases have been diagnosed since the syndrome was first identified in 1981¹ and this number is predicted to increase to over 270,000 by 1991.² The number of AIDS

cases in Rhode Island has risen ten-fold since 1983³ and is predicted to steadily increase in the future. Also, since patients with AIDS come from subgroups that previously have had low rates of hospitalization, the AIDS epidemic has resulted in an increased workload for hospitals.⁴

Physicians are in an excellent position to influence the mental as well as physical health of those with AIDS. Specifically, physicians have the responsibility of counselling HIV-infected patients, educating those patients who engage in high risk behaviors, advising those who have tested negative but have concerns, and treating patients with AIDS.^{5, 6} In addition, they are called upon to educate the community about the dangers of AIDS.⁷ It is for this reason that educational material should be developed and distributed to physicians which will keep them informed and thus able in turn, optimally to assist their patients.

To facilitate planning for physician education, Rhode Island Hospital (RIH) physicians were surveyed to determine: (a) their level of activity in treating HIV-infected patients, (b) the information physicians need and in what form they feel would be best suited for them, and (c) their perception of how AIDS will impact their practice.

Since the Rhode Island Hospital provides primary and tertiary health-care to a diverse population throughout the state of Rhode Island, it was chosen as the data gathering base.

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Vincent J. Barone, PhD, is a Fellow with the Brown University Program in Medicine and Department of Child & Family Psychiatry at Rhode Island Hospital, Providence, Rhode Island.

Method

Participants

The entire 807 Rhode Island Hospital medical staff were mailed questionnaires during the summer of 1988. Of the 807 Rhode Island Hospital medical staff surveyed, 395 responded (48.9 per cent). The specialties of the physicians were diverse (table 1). House staff were not included in the survey.

Procedure

Two mailings of the questionnaire were sent, each with a postpaid return envelope attached. Physicians were asked to respond as quickly as possible. Instructions were as follows:

The Rhode Island Hospital AIDS Task Force is assessing Staff Association members' needs for AIDS education. It is important to learn what information will be of most use to you. Please help us help you by completing this brief, confidential survey and mailing it back today. You need not sign the survey. Results and plans to provide information will be shared with all members of the Rhode Island Hospital medical staff.

Returned questionnaires were directly mailed to Rhode Island Hospital. All returned questionnaires were collated and frequencies were generated for each question.

The questionnaire consisted of 23 short-answer and multiple-choice questions. Of the 23 questions 7 asked about experience with treating HIV-infected patients, and counselling HIV infected patients. In addition, the physician was asked whether he thought that his treatment of HIV-infected patients might cause other patients to leave his practice. Four questions asked about perceived risks of transmission, knowledge and use of universal precautions. There was one open-ended question which asked the question, "Is there anything else RIH should be doing for you regarding AIDS?" The remaining questions sur-

Table 1. Physician Specialties (n = 395)

Specialty	No. of physicians in our sample (n = 395)
Medicine	134
Pediatrics	67
Psychiatry	17
Surgery	81
Ob-Gyn	15
Other	42

veyed physicians' preference regarding the amount and form of AIDS information.

Results

Nearly half of the physicians surveyed care for HIV-infected patients. Slightly more than half of the physicians surveyed were asked questions dealing with AIDS by their patients, and, of these, approximately 66 per cent feel prepared to answer patient questions concerning AIDS. Some physicians believe they will lose patients if the patients know that their physician treats people with AIDS. Table 2 outlines physicians' attitudes and beliefs about AIDS.

Two-thirds of the physicians surveyed feel they conduct procedures that place the physician at risk of contracting AIDS. Most feel knowledgeable about universal precautions and are confident they will not get AIDS if they follow these precautions.

At the time of the survey, over half of the surveyed physicians indicate they receive most of their information from professional board specialty sources and the American Medical Association. Even with these sources, physicians express a desire for more information from RIH. Well over half prefer a special newsletter as a source of AIDS information.

Table 2. Physicians' Attitudes and Beliefs about AIDS

	% Endorsed Total Sample (n = 395)
Patients ask about AIDS	56
Feels prepared to answer patients questions about AIDS	58
Feels would probably lose patients if they knew he/she treated PWA	15
Conducts procedures which place him/her at risk for AIDS	67
Concerned may acquire AIDS through professional exposure	64
Knows universal precautions	77
Confident will not get AIDS if follows universal precautions	82
Get AIDS information from:	
(1) Professional board specialty	68
(2) American Medical Association	50
Would like more information from RIH	60
Prefer a special newsletter as AIDS information source	58
Have talked with office staff about AIDS issues	65
Would encourage office staff to attend RIH seminars on AIDS	52
Believes AIDS will become more widespread	80

Furthermore, over two-thirds of physicians surveyed have talked to office staff about AIDS issues and slightly over half would encourage office staff to attend RIH seminars on AIDS if any were offered.

Responses to the open-ended question, "Is there anything else RIH should be doing for you regarding AIDS?," reflected three types of physician concerns. These are: a) Practical, procedural concerns (eg, "Provide impermeable gowns and adequate optical quality eyewear in operating room"); b) treatment problems (eg, "Fund social workers and nurse clinicians to help care for patients"); and c) the wish for RIH to take a leadership role (eg, "The hospital needs to take a firm position about confidentiality").

Discussion

Despite the small total number of AIDS cases in Rhode Island, over half of the RIH physicians surveyed treat HIV-infected patients. Furthermore, well over half are asked questions concerning AIDS by their patients. These responses highlight the current extent of physician exposure to HIV issues. However, only about two-thirds of physicians feel prepared to answer patients questions regarding AIDS. Perhaps this is indicative of the complexity of AIDS issues. A similar survey performed by the Minnesota Department of Health (MDH) found that 35 per cent of physicians surveyed had experience treating HIV-infected patients or patients with AIDS. Based on their findings and the percentage of physicians who treat AIDS or HIV-infected patients, the MDH recommends that additional physician education occur.⁹

The need for specific physician education has been formally set forth by various professional organizations. Linda Brooks, former Director of Infection Control and Environmental Safety for the American Hospital Association (AHA), says "It is now more important than ever that hospitals take a leadership role in the educational effort because of the misinformation about AIDS that is being released through the media."⁸ The American Medical Association (AMA) has developed a three tier program designed to educate physicians, that consists of: a) The direct education of physicians about AIDS; b) training of physicians to be community educators; and c) AMA education and interaction with community leaders.^{9, 10, 11} The American College of Physicians and the Infectious Diseases Society of America encourage physicians to take complete sexual histories and provide candid risk-reduc-

tion education for high risk patients.^{9, 12} Also, the Physicians Association for AIDS Care has released a news journal that addresses the diversity of clinical, ethical, social, economic, and political dimensions of the HIV epidemic (Physicians Association for AIDS Care, 101 West Grand Avenue, Suite 200, Chicago, IL 60610).¹³

Locally, the Brown University AIDS Program (BRUNAP) has a subcontract from the AIDS Education and Training Center at the University of Massachusetts to train physicians and other primary care providers in the treatment of AIDS and HIV infection. BRUNAP trains approximately 25 providers every six months, in issues ranging from clinical work-up and antiviral treatment of an infected patient, to the legal ramifications of AIDS legislation. (For further information, coordinator Joseph Copeland can be reached at Memorial Hospital, (401) 722-6000, ext. 2602).¹⁴ The Rhode Island Department of Health is very active in AIDS education through promotion of speakers and materials. They have recently developed a physicians guide to AIDS which will be published and ready for distribution in the spring of 1989. Also, an AIDS conference, developed specifically for physicians, was held on May 24, 1989 (through the Rhode Island Department of Health Infectious Diseases). As of now there is no specific newsletter devoted to AIDS available locally, although one would clearly appeal to physicians.

Recognizing the increasing number of HIV-infected patients and the concomitant impact on physicians and other health-care workers, RIH is further developing educational programs. (The results of this survey have been shared with Barbara DeBuono, MD, Medical Director of the Disease Control Section at the Rhode Island Department of Health.) The indication of physicians' preference for a newsletter as the information vehicle of choice reinforces the Health Department decision to publish its new quarterly AIDS newsletter for physicians throughout the state. Also in response to this physician preference, the RIH AIDS Task Force chair will contribute information to the hospital's Physicians Newsletter. RIH-All Hours, the hospital's internal publication which has a monthly distribution of 7,000, will continue its commitment to an AIDS information column.

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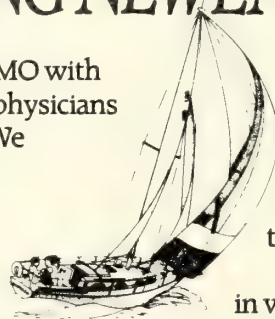
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Dr. Holwick outside of hospital where she practices as a civilian traumatologist



Dr. Holwick in operating room at Letterman Army Medical Center.

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Captain, U.S. Army Reserve.

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University of California School of Medicine.

RESIDENCY Harbor General Hospital – UCLA
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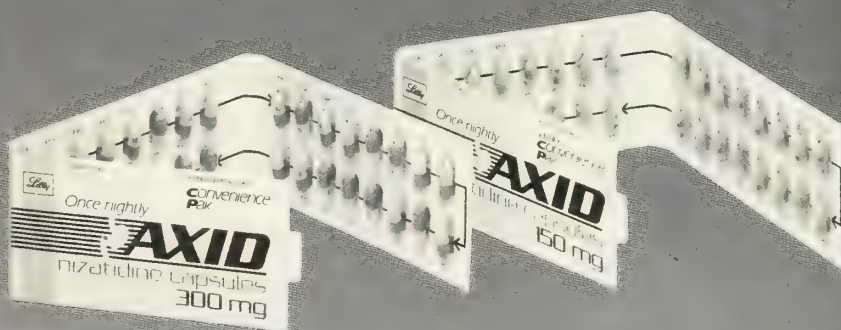
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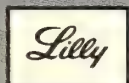
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Precautions: General – 1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.
2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency.

3. Pharmacokinetic studies in patients with hepatorenal syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests: False-positive tests for urobilinogen with Multistix® may occur during therapy with nizatidine.

Drug Interactions: No interactions have been observed between Axid and theophylline, chlorazepate, lorazepam, diazepam, phenytoin, and warfarin. Axid does not inhibit the cytochrome P 450 linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high dose males was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding of adenomas only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a two-generation prenatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy – Teratogenic Effects: – Pregnancy Category C – Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect, but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Studies conducted in lactating women have shown that <0.1% of the administered oral dose of nizatidine is secreted in human milk in proportion to plasma concentrations. Caution should be exercised when administering nizatidine to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo. Among reported adverse events in the domestic placebo-controlled trials, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A variety of less common events was also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic: Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients and was possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L) and, in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrence of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular: In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

CNS: Rare cases of reversible mental confusion have been reported.

Endocrine: Clinical pharmacology studies and controlled clinical trials showed no evidence of androgenic activity due to Axid. Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic: Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H₂-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumentary: Sweating and urticaria were reported significantly more frequently in nizatidine than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity: As with other H₂-receptor antagonists, rare cases of anaphylaxis following administration of nizatidine have been reported. Because cross-sensitivity in this class of compounds has been observed, H₂-receptor antagonists should not be administered to individuals with a history of previous hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other: Hyperuricemia unassociated with gout or neoplasms was reported. Eosinophilia, fever, and nausea related to nizatidine administration have been reported.

Overdosage: Overdoses of Axid have been reported rarely. The following is provided to serve as a guide should such an overdose be encountered.

Signs and Symptoms: There is little clinical experience with overdosage of Axid in humans. Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous median lethal doses in the rat and mouse were 301 mg/kg and 232 mg/kg, respectively.

Treatment: To obtain up-to-date information about the treatment of overdose, a good resource is your certified regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the Physicians' Desk Reference (PDR). In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance.

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THE RHODE ISLAND MEDICAL JOURNAL

The Official Organ of the Rhode Island Medical Society
Issued Monthly under the direction of the Publication Committee

VOLUME I
NUMBER 1

PROVIDENCE, R. I., JANUARY, 1917

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THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

Under its current title, the *Rhode Island Medical Journal* has been publishing at monthly intervals for 73 uninterrupted years. The contents of these 871 past issues represent a distillation of our history as an honored profession and reflect in microcosm the progress of medicine in Rhode Island during this century. Our problems, aspirations, struggles, concerns and anxieties, imagined or realized, form the basis for countless editorials appearing during these seven decades. This printed heritage also embraces numerous articles by our members, contributions by internationally noted physicians and scientists, vital statistics of the state of Rhode Island, synopses of our business meetings, the accomplishments of certain members, and the customary miscellany which provide such a vital part of any organizational journal. To read these older issues is to be both inspired by the accurate predictions of some contributions — and humbled by the incorrectness of others. Clearly, our professional history did not begin with yesterday's local newspaper.

The editors of the *Rhode Island Medical Journal* believe that the legacy of our publication is an important part of our identity. Accordingly, at about monthly intervals, the *Journal* will carry brief segments abstracted from the issues of twenty-five and fifty years ago. These short summaries will serve to demonstrate how far we have advanced in certain arenas, and how little we have progressed in others. Furthermore, the problems which seem novel to us today may reveal themselves to be problems which equally burdened our colleagues decades ago. It is also instructive to observe how the spectrum of diseases has evolved during these decades and the

extent to which medical understanding has altered even our nomenclature. It is our hope that these synopses will be a source both of entertainment and education.

Fifty Years Ago (JUNE, 1939)

The *Journal* is edited at that time by Albert Miller, MD and the Associate Editors are: Charles Bradley, MD, William Buffum, MD, Alex Burgess, MD, Francis Chafee, MD, Cecil Dustin, MD, Henri Gauthier, MD, John Ham, MD, John Helfrich, MD, Ernest Thompson, MD, George Young, MD.

The lead article entitled, "Surgery in the Treatment of the Disorders of the Autonomic Nervous System" is a rigorously extensive review of the subject by a young surgeon named Seebert J. Goldowsky, MD who had graduated from medical school only a few years before this publication. In summary, the author notes: "The disorders which have responded to surgical procedures upon the autonomic nervous system are as follows: [1] Raynaud's disease and scleroderma. [2] Thrombo-angiitis obliterans. [3] Essential hyperhidrosis. [4] Chronic rheumatoid arthritis. Vasospasm and sweating. [5] Infantile paralysis. Vasospasm and sweating. [6] Erythrocyanosis associated with chronic chilblains. [7] Traumatic vasomotor neuroses and causalgia. [8] Idiopathic megacolon. [9] Dysmenorrhea. [10] Pelvic malignancy. [11] Angina pectoris. [12] Essential hypertension. [13] Carotid sinus syndrome. [14] Miscellaneous."

The lead editorial, entitled "The Product of a Hospital" notes: "In spite of the improved methods of diagnosis and treatment, the improvement in nursing, diminished maternal mortality, and freedom from the mortality of diphtheria, typhoid fever and the diarrhoeal diseases of childhood, some of our hospitals now show no such improvement in mortality statistics as would seem to justify the increased expense of hospital treatment. We offer as a topic for discussion the question as to whether these hospitals should be fairly judged by the height of their buildings, the magnificence of their operating equipment, the number of their X-ray machines, the extent of their laboratories or by their success or failure in the treatment of disease."

Vital statistics from the Health Department for April, 1939, show an overall mortality rate of 13.7/1,000, an infant mortality rate of 39.5/1,000 births and a birth rate of 21.5/1,000. The roster of communicable diseases list 7 deaths from pulmonary tuberculosis.

* * * * *

Twenty-Five Years Ago (JUNE, 1964)

The *Journal* is edited by Seebert J. Goldowsky, MD, and the Committee on Publications includes Alex Burgess, MD, John Gilman, MD, Seebert Goldowsky, MD, Robert Lewis, MD, Peter Mathieu, MD, Jose Ramos, MD, Laurence Senseman, MD, and Milton Hamolsky, MD.

The lead article is the 1963 Fiske Essay written by Hinderikus Zondag, MD, from the Netherlands, on the subject: "Enzyme Activity in Dysgerminoma and Seminoma." The article concludes: "[1] This paper reports on a clinical study of serum LDH-isoenzymes. Normal serum values are presented, and the isoenzyme distribution in human organs and tissues is given. [2] In about one-half of 150 cases with various neoplastic diseases a typical serum enzyme pattern was found with elevated LDH activity in the middle fractions. [3] In cases of seminoma testis and dysgerminoma of the ovary a special pattern of serum LDH appeared to exist, with high activity in LD₁ and LD₂. [4] The results are discussed and the conclusion is reached that the determination of LDH-isoenzymes can be an important aid in the diagnosis and follow-up of malignant diseases."

Another paper entitled, "Prognostic Significance of Myelography in Traction Injuries to the

Brachial Plexus" is written by Henry Litchman, MD and David Barry, MD.

The Presidential Address by the Society's President for 1963-64, Thomas Perry, Jr., MD, surveys the activities of the Society during the past year. Mention is made of a committee assigned to consider the feasibility of combining the Society's library with that at Brown University. Perry's address also comments on the enormous increase in public use of hospital emergency rooms [instead of doctor's offices], and states, "... a new committee with representatives from each hospital has been appointed to see if there is anything we, as doctors, should be doing to influence this trend."

"Another committee has met once with labor representatives to discuss their as yet embryo ideas of forming a group health association. In brief such an association would offer more services than the Blue plans and would be staffed largely by full-time physician employees. Those who attended this meeting came away with the impression that the individuals developing this plan are sincere in their efforts to offer a really good product, and if a good plan cannot be developed there probably won't be any at all."

The Presidential Address provides further observations on public service by the physicians of Rhode Island, and comments on *The National Scene* that, "... The Rhode Island Medical Society resolution on integration was defeated in the American Medical Association House of Delegates. . . . It hardly seems proper that an individual who has obtained his medical training should, because of color, be kept from the advantages, educational and otherwise, provided by our medical societies. Our resolution, with its punitive clause for societies not integrating, proved too strong. We believe its objectives will eventually be achieved. Our own House of Delegates has already voted its support of a New York civil rights resolution to be presented at the next American Medical Association meeting."

There is also discussion on impending federal legislation, such as the Kerr-Mills and the King-Anderson Bills both of which concern the controversial subject of medical care for the elderly.

The principal editorial addresses workmen's compensation medical costs and the allegations of the Providence newspaper that the burden of blame is with the physicians and "... the costs of the program discourages industry from locating in this state."

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BOOK REVIEW

Usher Parsons

Yankee Surgeon: The Life and Times of Usher Parsons, 1788-1868. Seebert J. Goldowsky, MD. Boston: Francis A. Countway Library of Medicine, 1988, 450 pp., \$24.50.

Whenever medical history in Rhode Island is discussed, the name of Usher Parsons, MD is apt to be in the forefront. He was the leading surgeon in the state in the first half of the 19th Century. His career encompasses, among other experiences, the Battle of Lake Erie in 1813, professorship in the first incarnation of the Brown University Medical School, the Dorr Rebellion, and active participation in the fledgling AMA, of which he was Acting President. It culminated with the attainment of one of his principal objectives, the opening of the Rhode Island Hospital in 1868.

Even in this century, accounts of his contributions have appeared many times in the *Rhode Island Medical Journal* in connection with early surgery, Brown University, the Rhode Island Hospital, and the Rhode Island Medical Society itself. But aside from a brief memoir of Parsons's life written by his son Charles in 1870, there has been no other full account of his life until now. Seebert Goldowsky's *Yankee Surgeon*, therefore, fills a void and does so handsomely. Dr Goldowsky has been writing this book for thirty years. As he has turned up more and more pertinent material about the subject, including two large treasure troves of memorabilia from New York State and Virginia, his horizons have widened. He has therefore had to start afresh on two occasions. The result is a beautiful volume that will be valued by anyone interested in New England history, most of all those of us with medical roots in Rhode Island. Parsons himself became an historian in later life, so that one moves with him into such fields as Rhode Island Indian lore and the Battle of Louisburg in 1745.

Some idea of the scholarship that has gone into this work comes from the fact that the seventeen chapters are accompanied by 1,024 references. These are conveniently placed at the chapter

ends, so that they do not clutter the text, but are easily reached when desired.

Dr Goldowsky's style makes for easy reading. His occasional brief remarks on Parsons's clinical performances and medical writings (he was a prolific writer for his time and place) point out the good and the bad, both in comparison to his contemporaries and to modern medicine.

Much of this book is truly gripping — the cannonballs coming through his surgery at Lake Erie, the story of his brief ill-fated marriage to Dr Oliver Wendell Holmes's sister, and the battle between the medical faculty and the Brown administration, among other things.

There are times, though, when Parsons's life was pretty humdrum. In the book these periods are enlivened by well-documented vignettes from the social life of Ohio, Boston, Providence, and elsewhere, as well as local and national political events. Parsons knew a great many important people of his time. Incidentally, medical politics in Rhode Island could be pretty vicious.

In the opinion of this reviewer *Yankee Surgeon* is easily the number one literary achievement by a Rhode Island physician in my lifetime.

Thomas Perry, Jr., MD



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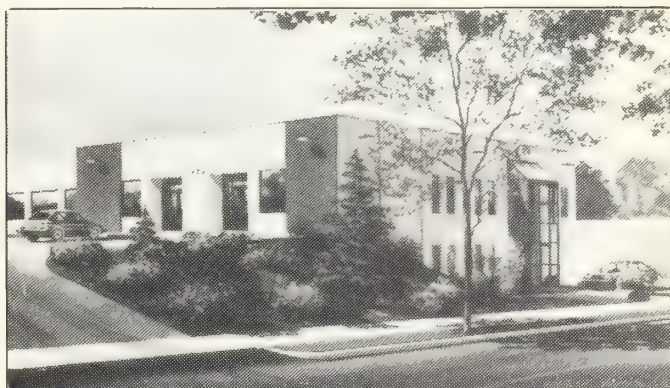
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YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon[®] is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

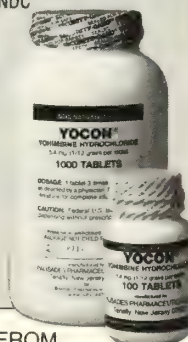
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon[®] 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

Rev. 1/85



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JULY 1989

The Memorial Hospital

Contact: (401)722-6000, ext. 2142

Date: MTWF
Time: 12:15 pm
Topic: Medicine/Family Medicine
Speaker: Multidisciplinary roster
Location: Sayles Conference Room #2 & #3

• • •

Date: Every other Monday
Time: 12:15 pm
Topic: Pulmonary Case Review
Speaker: Frederic G. Hoppin, MD and colleagues
Location: Sayles Conference Room #2 & #3

• • •

Date: Every Tuesday
Time: 8:00 am
Topic: Cardiology Conference
Speaker: Richard A. Carleton, MD and colleagues
Location: Sayles Conference Room #1

• • •

Date: Every Tuesday (except last Tuesday of month)
Time: 8:00 am
Topic: Hematology/Oncology Conference
Speaker: Manfred Steiner, MD and colleagues
Location: Immunology/Oncology Conference Room

• • •

Date: Last Tuesday of each month
Time: 7:30 am
Topic: Tumor Board Conference
Speaker: Manfred Steiner, MD and colleagues
Location: Physicians' Auditorium

• • •

Date: Every Wednesday
Time: 10:00 am
Topic: Medical Grand Rounds
Speaker: Distinguished Guest Speakers
Location: Physicians' Auditorium

Date: Every Wednesday
Time: 8:00 am
Topic: Pediatric Grand Rounds
Speaker: Louise S. Kiessling, MD and colleagues
Location: Physicians' Auditorium

• • •

Date: Every other Wednesday
Time: 12:15 pm
Topic: Infectious Diseases Conference
Speaker: Kenneth H. Mayer, MD and colleagues
Location: Sayles Conference Room #2 & #3

• • •

Date: Every Thursday
Time: 8:00 am
Topic: Surgical Grand Rounds — Surgical Mortality/Morbidity
Speaker: Stephen J. Hoyer, MD and colleagues
Location: Physicians' Auditorium

• • •

Date: Every Thursday
Time: 8:00 am
Topic: Orthopedic Conference
Speaker: Richard G. Bertini, MD and colleagues
Location: Sayles Conference Room #2

• • •

Date: Every Thursday
Time: 8:00 am
Topic: OB/Gyn Conference
Speaker: Ronald R. Ricco, MD and colleagues
Location: Sayles Conference Room #1

• • •

Date: Every Thursday
Time: 12:15 pm
Topic: Family Practice Grand Rounds
Speaker: Vincent R. Hunt, MD and colleagues
Location: Physicians' Auditorium

Institute of Mental Health

Contact: (401)464-2458

Date: July 13, 1989

Topic: Case Conference

Speaker: Lorin Mimless, MD — presenting
Matthew Edlund, MD — moderating

Location: Adolph Meyer Building
3rd floor conference center

Date: July 27, 1989

Topic: Case Conference

Speaker: Aimee Schwartz, MD — presenting
Eileen McNamara, MD — moderating

Location: Adolph Meyer Building
3rd floor conference center

• • •

Butler Hospital

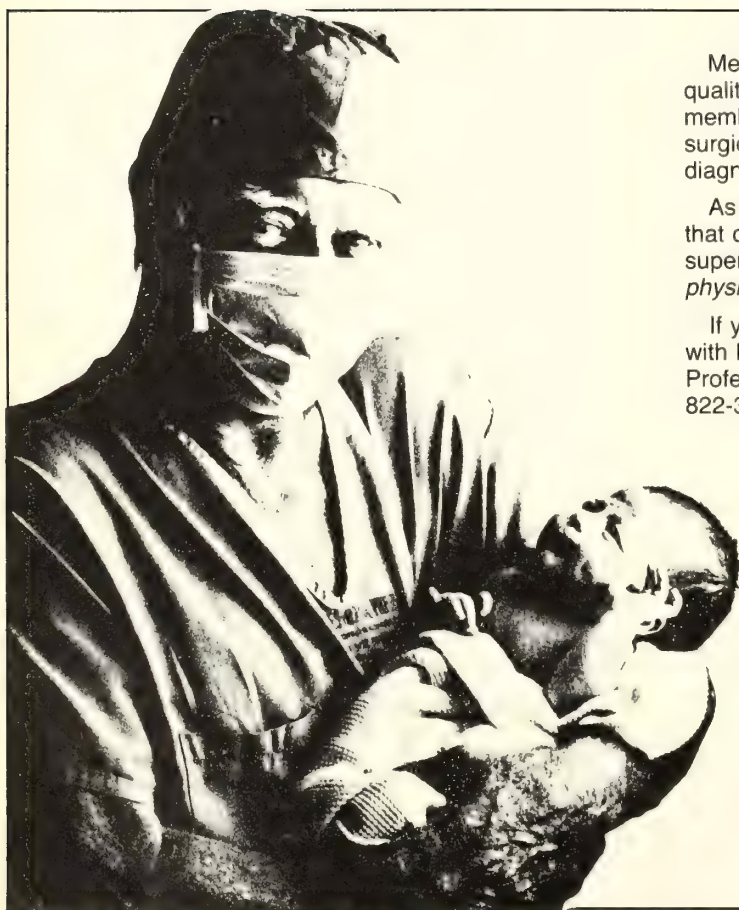
Contact: (401) 456-3750

Date: Friday, July 28 and Saturday, July 29, 1989

Topic: "Computers in Neuropsychology:
Applications in Assessment & Rehabilitation"

Location: Center for Information Technology,
Brown University

• • •



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References: References should be limited to those citations noted in the text. The references must be typed double-spaced and numbered as they appear consecutively in the text, with their positions clearly indicated in the text. All references must be checked to assure complete accuracy. Each journal reference must include the full name of the author(s); complete title of paper; name of publication; volume number; issue number; first and last page of paper; and date (year, month, and day as indicated). Each book reference must include the full name of author(s), editor(s), or both, with initials; title of book; edition; publisher; location; year of publication, volume (if given); and page number. If the reference is to a chapter within a book, the author of the chapter, if different than the author of the book, and the title of the chapter (if any) must be provided.

It is rarely desirable to include a complete review of the literature in the references. An alphabetized bibliography is to be used only when the listing is of books suggested for supplementary reading.

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VASOTEC®

ENALAPRIL MALEATE | MSD

Contraindications: VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Warnings: **Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Heart failure patients given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy (See DOSAGE AND ADMINISTRATION). Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in heart failure patients), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: **General: Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: Elevated serum potassium (> 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See Drug Interactions.)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyl-dopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium: A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. Although a causal relationship has not been established, it is recommended that caution be exercised when lithium is used concomitantly with VASOTEC and serum lithium levels should be monitored frequently.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters.

There are no adequate and well-controlled studies in pregnant women. VASOTEC® (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Milk in lactating rats contains radioactivity following administration of 14 C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 298/ patients.

Hypertension: The most frequent clinical adverse experiences in controlled trials were headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthma (1.1%).

Heart Failure: The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthma (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

Cardiovascular: Myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, Hypotension), cardiac arrest, pulmonary embolism and infarction, rhythm disturbances, atrial fibrillation, palpitation.

Digestive: Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis.

Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION), prostate hypertrophy.

Respiratory: Bronchospasm, rhinorrhea, asthma, upper respiratory infection.

Skin: Herpes zoster, pruritus, alopecia, flushing, photosensitivity.

Other: Muscle cramps, hyperhidrosis, impotence, blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include fever, myalgia, and arthralgia, an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Clinical Laboratory Test Findings:

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g % and 1.0 vol %, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

Dosage and Administration: **Hypertension:** In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Hypertensive Patients with Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure: VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects.) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

Dosage Adjustment in Heart Failure Patients with Renal Impairment or Hyponatremia: In heart failure patients with hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine > 1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, Heart Failure, WARNINGS, and PRECAUTIONS, Drug Interactions.) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

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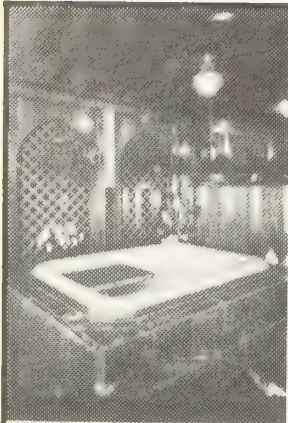
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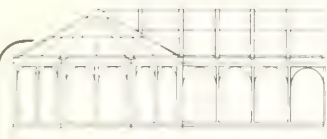
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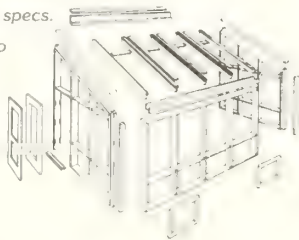
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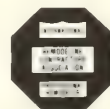
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Cover: *This month's issue of the Journal is devoted to Hospice Care in Rhode Island. Pictured on the cover are (l to r) Henry C. McDuff, Jr, MD, Medical Director of Hospice Care of Rhode Island; Hospice patient Thomas McKenna of Warwick; and Mary Kate Grzebien-Carpenter, RN, Patient Care Coordinator. Standing behind Mr. McKenna is Patricia Sollois, Home Health Aide. Photo by Charles Anderson, Director of Public Relations, Hospice Care of Rhode Island.*



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Care for the Terminally Ill

Hospice, as an organized system providing coordinated, compassionate care for the dying patient, is less than three decades old. None of the separate elements which Dr C. Saunders had assembled at St Christopher's Hospice were novel. Each component of her program — palliative rather than curative effort, the centrality of the patient and family in decision-making, the employment of an interdisciplinary team with the physician as a member rather than leader — had certainly been adopted by countless physicians when they were each confronted with a hopelessly ill person with cancer. And yet, curiously, no coordinated program enunciating this philosophy had been established until Saunders began her work in the 1960s. But once begun, the hospice movement spread rapidly, mainly in English speaking nations, until today there are over 1,500 hospice programs in the United States alone. While the hospice movement had been started by a physician, its initial support came rather from the clergy and from nurses. Only in recent years has the movement been incorporated into the mainstream of health care.

To some physicians, the use of hospice appeared to be an admission of professional defeat, a departure from the physician's obligation to prolong life. Certainly in the last half-century the accumulated therapeutic successes achieved by medicine have been nothing short of astonishing. Many diseases thought to be incurable five decades ago have since yielded to the advances of biomedical science. Inevitably, therefore, some have concluded that no disease was truly incurable; there were only disorders awaiting a cure in the near future. But for the dying patient, the near future holds only the prospect of pain, anxiety and abandonment.

Physicians have come to recognize that a residue of illnesses, notably neoplastic, are for the moment truly incurable and that aggressive intervention in such patients will serve only to increase their discomfort, confine them to an inhumane environment and effectively remove them from their families; and physicians have

recognized further that there is, indeed, a critically important palliative and nurturing role which the medical profession can and should fulfill when cure is no longer a rational goal.

What is the extent of need for such a nurturing rather than curing program? The American Cancer Society estimates that there will be 4,900 new cases of cancer in Rhode Island during the year 1989. And in this same year there will be an estimated 2,500 Rhode Islanders dying of endstage cancer. The need for a system, involving physicians, to ease the pain and sorrow of these patients is not in dispute. Certainly the alternatives are no longer acceptable: death in the home without skilled support or pain control; or a lonely death in an expensive, depersonalized hospital setting.

Increasingly, then, the hospice alternative has been adopted by many of Rhode Island's physicians. It is estimated that the hospice programs now provide continuing care for one out of every four cancer deaths in this state.

The current issue of the *Journal* is devoted in its entirety to a consideration of hospice and its role in the health care system of Rhode Island. The lead article, by the Executive Director of Hospice Care of Rhode Island (the largest of the hospices within the state), outlines the growth and maturation of the hospice effort within the nation as well as within this state. The article by Dr. Henry McDuff, the Medical Director of Hospice Care, describes the patient population seeking help from hospice, the medical nature of hospice care and its relationship to the primary physician. The third article discusses the pharmacological means of allaying the many vexing symptoms which accompany terminal cancer. And finally, there are two brief and personal commentaries, written by practicing nurses in the Rhode Island community, summarizing their remembrances of the human dimensions of dying and the role of hospice in easing the accompaniments of despair, anguish and grief.

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Hospice Care of Rhode Island: Past, Present and Future

David W. Rehm, MSS, ACSW

... The early hospice movement foresaw the growing role of the patient as informed and active consumer, rather than passive recipient.

The development of Hospice Care of Rhode Island (HCRI) parallels this country's hospice experience. It began outside of, and in many ways, in opposition to the traditional system of medical care for the terminally ill. The early founders were concerned about articulating a system of values nourished by a purity of purpose and vision. Only much later and with much trepidation did the hospice movement become a part of Rhode Island's and this country's health care system. Like any new group it first defined itself in opposition to the establishment. This "outside" status was both a problem, and a source of strength which helped bind the group together and define its identity. The positive legacy of this era is a maturing but clearly articulated belief system that remains the force behind HCRI today. These values were and are:

1. A commitment to not compromise the quality and depth of life by efforts to sustain it.
2. The patient and family are in control of all care decisions. Our role is to support and help implement their decisions, not to exert outside influence or control.
3. Hospice seeks to care for the whole person. We seek to address his/her spiritual, emotional, physical, and social needs.

David W. Rehm, MSS, ACSW, is the Executive Director for Hospice Care of Rhode Island, Providence, Rhode Island.

Much of the success of the hospice movement is based on the timeliness of this value system. It anticipated the ethical dilemmas of our expanding medical technology. It foresaw the growing role of the patient as informed and active consumer, rather than passive recipient. It foreshadowed our growing awareness of the effect of emotional, spiritual and social factors on a person's physical condition.

During its early years, HCRI relied almost exclusively on volunteers. Its client services were largely limited to emotional, spiritual and social support. Funding came from grants and donations, and so medical services and supplies were very limited. The organization's stakeholders were limited to board, volunteers and those patients and families served by the program. Health care providers, funders, and professionals were for the most part unaware of or indifferent to the fledgling agency that was HCRI. The organization was, therefore, largely driven by the vision of its board and volunteers. Its patterns of service were flexible, adapting frequently to the needs of those patients electing palliative rather than aggressive forms of treatment. Admission was also limited only to cancer patients.

Within that early value framework was, however, a potential conflict that has only recently been resolved. The emphasis on quality of life versus longevity had within it a perception of what a "good death" should be like. The patient should be able to confront his own terminality in the context of a caring and supportive family system. While the organization quickly learned that this was not always possible, this model of a successful hospice care began to exert a subtle influence on patient selection that would only become clear years later. This model of the "good patient," although subtle and implicit, would later prove to be in conflict with the second value of

patient decision-making and control. In the early stages the emphasis was on the quality of life. Much energy and attention went into exploring and defining that vision. Since the capacity of the program could not approach the level of need at that time, it was only natural that hospices would selectively admit those patients who shared its definition of quality of life.

This model of care also tempered HCRI's early relationship with the medical community. Physicians frequently perceived hospice as wanting to take their patient away. While this was never technically true (primary physicians have always maintained their role with the patient), it was true that there was a subtle desire to assume control of the patient's care. This model of a "good death" not only selected certain patients for admission but also prescribed the model of care for their physicians. Certain forms of treatment, because of their side effects, were seen as universally undesirable (most frequently chemotherapy and radiation). The agency's early stance as an antagonistic outsider to the health care establishment, magnified these perceptions. This must be understood, moreover, in light of the need of a fledgling movement and organization to establish a clear identity and philosophy. In fact, it was this same conviction and clarity of purpose that allowed HCRI to survive its early struggles and exert a growing and healthy influence on the care of Rhode Island's terminally ill. The negative side to this was that HCRI would come out of this period with a somewhat inflexible formula for its pattern of rendered care as well as the type of patient appropriate to receive it.

In the mid 1980s, HCRI and hospices nationally were entering a phase of rapid growth forcing the first of two significant watershed decisions. Nationally, hospice leaders had been pressing Medicare to adopt coverage for hospice services and locally the leadership of HCRI had been working for recognition by Blue Cross and the HMOs. By then the economy was deeply into the era of health care cost containment and so the case was made on the grounds that hospice care was not only a humane and needed service but also a cost-effective alternative to traditional terminal care. The decision to pursue third-party funding was a difficult and critical one. Across the country, and in the board and staff meetings of HCRI, anguished discussions were held over the wisdom of such a course. Would it merely expand the availability of hospice care as we knew it or would it change that care and corrupt the purity of the still newly forged vision? Would

HCRI, which had grown largely outside of, and in opposition to, the traditional healthcare system, become merely another of its components directed and controlled by third-party rates and regulations? Ultimately, of course, our adolescent ambivalence was overcome and the decision to pursue third-party recognition and health care licensure was adopted. What ensued was a dramatic period of growth that continues to this day. In 1983, 98 patients were admitted to HCRI's program while in 1989 well over 500 will be served. But the growth has not been in size of the program alone. HCRI status has changed from "outside" to "inside." In fact the Hospice Medicare benefit requires us to assume the financial and care management responsibility for nearly all care related to the patient's terminal illness. HCRI rapidly moved from a largely volunteer organization providing spiritual, emotional and social support to a full-service medical home care provider. Professional staff was hired. Purchase of service contracts were developed with hospitals, nursing homes, pharmacies, equipment suppliers, and home health agencies. Billing and accounting systems were developed and policies and procedures codified. In short, in a very brief time, HCRI moved from an unfettered grass-roots organization to a full-service health care provider. Rapidly our adolescence was becoming but a fond memory.

The organization now had acquired many more stakeholders which complicated what had been a relatively simple agenda. These included third-party insurers, state regulators, primary physicians, hospitals, and service providers. The organization's goals began to expand beyond the immediate goals of patient care to include cost effectiveness, greater responsiveness to physicians and institutions, and participation in creating a better state health care system.

We became much more sophisticated, our world much more complicated, but were we "corrupted?" Yes and no. Unquestionably during this period, HCRI became focused on learning to operate successfully in this system. Decisions had to be made within the constraints of third-party coverages and cost containment became critical to survival. As a result the definition of a "good hospice patient" began to be shaped by the forces of the third-party system. Difficult and complicated cases now represented a threat to the agency's fiscal survival. Admission did gradually become more open, however, as the infusion of new funds eliminated the need for a waiting list. A tension was created by the capacity to admit more

patients since this larger group included patients with marginal family systems and more complicated medical needs which meant greater financial risk to the agency. In spite of these new sources of internal tension and a more complex array of goals and stakeholders, the original value system continued to provide the foundation necessary to address these issues. Against the background of this experience HCRI confronted its next watershed decision.

HCRI like most hospices, was dedicated to the care of cancer patients exclusively. This mission was challenged by the emergence of AIDS as a local health concern. In 1985 HCRI received its first referral of an AIDS patient. The board responded by removing the diagnostic restriction to cancer patients from its mission statement. In so doing HCRI opened its program not only to persons with AIDS but to all other terminally ill patients as well. We were now confronted with patients who were very different from our previous experience. They required more skilled nursing and more complex treatments. They were much younger and so were less willing to forego aggressive treatment plans. They often had little or no family to support them. In short, they forced us to review many of our policies, practices, and admission criteria. Eventually this process led us back to that original value framework. The value that gave control to the patient and family took on a new importance. We began to see that it was the patients who must define for themselves what "quality of life" meant, even if it involved what occasionally appeared to us to be pointlessly intrusive treatment methods. We became more flexible about requiring a stable caregiver system. The overall result has been a healthy re-examination of our mission, values, policies, practices, and goals. HCRI has begun to return to the responsiveness and flexibility that characterized its earliest years. What is different is that we are no longer focused solely on the needs of the cancer patient but have become a mature partner in the Rhode Island health care system, addressing the needs of the physicians, hospitals, third-party insurers, nursing homes, and the system as a whole. The terminally ill of Rhode Island and their families remain, of course, our primary focus but that group has become larger, more varied, and with differing needs. As a result while our values have been scrutinized and somewhat redefined, they remain intact, strong, and clear. The board and staff have rededicated themselves to our mission, and we have asked the community to support us financially to

preserve our institutional independence. Physicians now find us as flexible partners offering an alternative which they can share with their patients when cure is no longer deemed possible.

It is from this revitalized base that we face the future. Our current goals include:

- 1) To expand in order to keep pace with the growing need. While our present status of 80 patient census, 40 staff, and \$1.7 million annual budget seem large, the projected need is more than double that. We must reach out to those new patients and raise the funds to care for them.
- 2) To develop the capacity to bring hospice to patients without caregivers (ie, without close relatives or friends). This is a rapidly growing population and our plans include offering more in home support, congregate living sites, and the building of a free-standing hospice facility for Rhode Islanders.
- 3) To develop specialized services to care for persons with AIDS. HCRI is working with other providers and agencies to develop an effective, coordinated response to these patients.
- 4) To develop specialized hospice services for children. The number of terminally ill children referred to HCRI is growing rapidly. We will work to best meet the needs of these children and their families.

Perhaps the adoption of this plan will prove to be another watershed decision for HCRI. What is clear is that it holds both excitement and challenge for us all.

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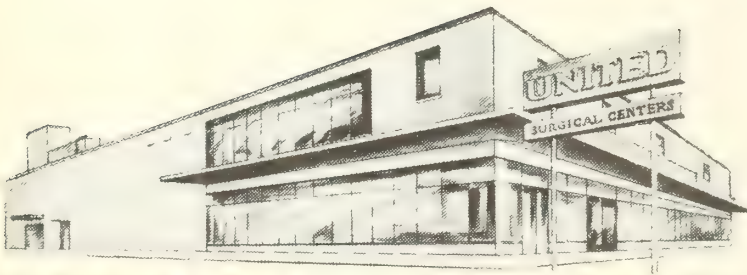
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Hospice Care of Rhode Island: 1989

Henry C. McDuff, MD, FACS, FACOG

... Hospice Care recognizes the critical importance of family relationships, supports the concept of palliative care and pain control but denies the intervention of inappropriate treatment which promises little success while frequently increasing patient discomfort.

Hospice Care of Rhode Island (HCRI) provides primary medical care for the terminally ill. In so doing, it acknowledges a role reversal: The patient and his family are in charge while the physician exerts an important but secondary role. It recognizes the critical importance of family relationships. It supports the concept of palliative care and pain control but denies the intervention of inappropriate treatment which promises little success while frequently increasing patient discomfort.

The criteria for admission to HCRI are: (1) Both patient and family want hospice; (2) the primary physician agrees with the precepts of hospice; (3) the patient suffers from a progressive, irreversible disease with a prognosis of six months or less; (4) the patient and family are aware of the diagnosis and prognosis; and (5) there is an identifiable primary caregiver.

History of the Hospice Movement

The word hospice is derived from the Latin *hospes*, meaning host or guest but is extended to include strangers and the place where they may derive comfort.¹ There are several older references to hospice, particularly during the times of the cru-

sades, describing places of rest on the pathway to the Holy Land.²

Dame Cecily Saunders, now Director Emeritus of St Christopher's Hospice in Sydenham, England, was the founder of the modern hospice movement. She had graduated from nursing school in 1941 but later resumed her formal studies in 1944 to become an almoner (social worker). In the years which followed she noted with distress the indifferent care given to terminally ill cancer patients and returned to Oxford University at age 33 to begin her medical studies. She was awarded a medical degree with honors in 1957.

Saunders' early pharmacologic research was conducted at St Thomas' Hospital. She soon transferred her interests to St Joseph's Hospice in South London, an institution managed by the Sisters of Christian Charity and dedicated to the care of the terminally ill cancer patient, many of whom suffered severe pain. The staff at St Joseph's viewed death and dying openly; they considered death as life's last journey.³

St. Christopher's Hospice, conceived by Dr Saunders, received its first patient in June of 1967. The facility has served as a model of compassionate care for the hundreds of hospices throughout the world which have since developed and flourished.³ The hospice model has also been widely adopted in Canada. The first hospice in the United States was established in New Haven, in 1974. Initially this had been a home care program, but it expanded to include an inpatient facility in 1980. By 1989 there were more than 1,500 hospice programs established in the United States.

Hospice Care of Rhode Island was conceived in 1975 and incorporated as a non-profit organization in March of 1976 with Rev Charles Baldwin as its first president and Rev Kenneth Wentzel as its consultant.^{4,5,6} The first patient, Mrs Mary M., was admitted in March of 1979. During its first six months, 13 patients were admitted, about one every two weeks. By the fifth year, in 1983, 100 patients had been admitted, at a rate

Henry C. McDuff, MD, FACS, FACOG, is Clinical Professor Emeritus, Brown University Program in Medicine and Medical Director for Hospice Care of Rhode Island, Providence, Rhode Island.

Table 1. Hospice Care of Rhode Island
A Statistical Profile

	1985	1986	1987	1988	1989*
No. new patients per year	201	310	367	434	500
Average daily census	31.0	48.4	53.5	63.9	73.8
Average length of stay (days)	71	70	75	59	54
Total no. patient days	11,495	17,682	19,536	22,444	23,500

* Estimates

of about two patients per week. In 1987, 262 patients were admitted, a rate of about five patients per week. And admissions for the current year of 1989 will likely exceed 500 patients, almost ten new patients per week.

HCRI is now the second largest hospice facility in New England with an active daily census of about 80 patients.

Table 1 illustrates the number of patients cared for by HCRI in the last five years. Table 2 identifies the increasing numbers of patients who have elected the Hospice Medicare Benefit since it became available in May, 1984. HCRI is obliged to present this health care option to all patients who have Medicare Part A coverage, and it is estimated that 350 patients will choose this plan during the current year. The mandated requirements for this plan are summarized in Table 3 and the differences between regular Medicare and Hospice Medicare detailed in Table 4.

Patient Population

For admission to the program, the patients must be afflicted with a progressive, unrelenting disease with a life expectancy estimated to be six or

fewer months. While the great majority (92 per cent) of hospice patients have advanced, disseminated cancer, some are afflicted with irreversible renal, pulmonic or neurologic disease and now, increasingly, AIDS. Hospice is not restricted to the elderly. While the mean age on admission to HCRI is currently about 67 years, young children as well as the very elderly have been and are admitted.

Referrals to HCRI come from diverse sources: physicians, nurses, social workers, clergy, hospital discharge planning teams, relatives, friends, and occasionally the patient himself/herself. All referrals are carefully evaluated by the admitting staff as well as the Medical Director. The primary physician is then contacted to determine whether admission to the program is medically appropriate. When the patient is admitted, HCRI works with and under the orders of the primary physician.⁷

What Is Hospice Care?

Hospice is dedicated to the belief that terminally ill persons be allowed to spend their final days as normally, as productively, as meaningfully as possible. Hospice identifies the family as the primary unit of care and centers most of its caring process in the home.⁸ Hospice seeks to enable the patient to live an alert, pain-free existence. HCRI offers a multidisciplinary team approach with home health aides and home nursing visits at whatever frequency is required throughout the day and night and on all days of the week. The number of nursing and health aide visits for the current year will likely exceed 11,000 (Table 2).

HCRI physicians make house calls in cooperation with the primary physician as do the social workers on our Patient Advocacy staff (Table 2). HCRI patients occasionally require special forms of care given at the bedside by physiotherapists, nutritionists and speech therapists. Pastoral

Table 2. Hospice Care of Rhode Island
The Growth of Provided Services in the Home

	1983	1984	1985	1986	1987	1988	1989*
No. patients	98	150	201	310	367	434	500
No. hospice-medicare	0	5	46	83	119	258	350
Nursing visits	345	2272	2590	2654	3780	5046	5050
Health aide visits	1435	2270	3537	4980	4515	5700	6028
Physician visits†					50	244	338
Social service visits	26	36	240	386	243	324	400

* Estimates

† numbers not available for years 1983-86.

Table 3. Requirements for Hospice Medicare Option

1. Patient must have Medicare, Part A.
2. Care must be palliative not curative.
3. No chemotherapy or radiation therapy are to be used except for palliation.
4. The patient, family and primary physician understand that all orders must be approved by the hospice medical director.
5. Patient must use only hospice contracted hospitals, laboratories, X-ray facilities, nursing homes, pharmacies and ambulance services; and that all bills are to be paid by hospice.

counseling by members of the clergy working with HCRI also represent an important component of compassionate care. HCRI has at its core a large body of trained volunteers who fulfill many functions needed to allow the agency to meet its obligations. These volunteer functions include patient assistance, feeding, transportation and, most important, companionship. During the year 1989, an estimated 8,500 volunteer hours will be recorded.

The daily medical care is rendered in concert with the orders of the primary physician. The palliative nature of this care is mutually agreed upon by the patient, the family and the primary physician. There have been occasions when patients or families change their minds and request more aggressive therapies, but this is rare. Few hospice patients require hospitalization and 87 per cent of the HCRI patients die in their homes surrounded by the ministering care and love which only families can provide.

Table 4. Differences Between Usual Medicare and Hospice-Medicare

Service	Medicare	Hospice-Medicare
Nursing visits	only if skilled	yes
Physician visits	80% with \$200 deductible	yes
Home health care aides	yes	yes
Medical equipment PT, OT, Speech therapy	yes requires Part B	yes
Laboratory tests	yes	yes
Diagnostic X-rays	yes	yes
Total nursing coverage	no	yes
Pharmacy costs	no	yes*
Crisis hospitalization	yes	yes
Nursing home respite, 5 days	no	yes
Ambulance service	to hosp. only	yes
Patient activity	home-bound	no restriction

* Hospice pays for all drugs related to the hospice admission diagnosis.

The role of HCRI does not cease with the death of the patient. Bereavement counselling is conducted with the family for as long as an additional year.

It is essential that the Medical Director of HCRI establish and maintain a close and mutually respectful relationship with the primary physician. The nurses, social workers and volunteers need uninterrupted support in their tasks and it is therefore vital that the HCRI medical staff remain visible and available. The medical staff has a further obligation to offer education concerning hospice care. The explicit duties of the Medical Director include: (1) Approve admission to HCRI, in concert with primary physician; (2) serve as a resource to HCRI nursing staff; (3) serve on local and regional committees and develop educational programs for professional and lay groups; (4) chair the Medical Advisory Committee of HCRI; (5) develop a cadre of HCRI physicians; (6) assist the primary physician in the daily care of the HCRI patient, including house calls; (7) be on call for any of the patients by means of a paging system; (8) fulfill various administrative duties including attendance at all patient review sessions.

Summary

Hospice care is an extension of primary care expressly designed to meet the human needs of the terminally ill patients and their families. Its nurses, volunteers, social workers, clergy and physicians, working collaboratively with the primary physician, seek to keep each patient free of pain, in a humane environment and to meet, where possible, immediate social needs.

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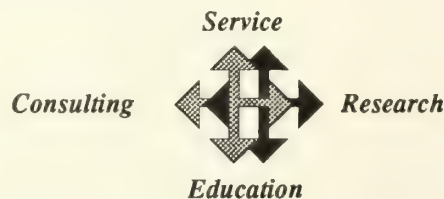
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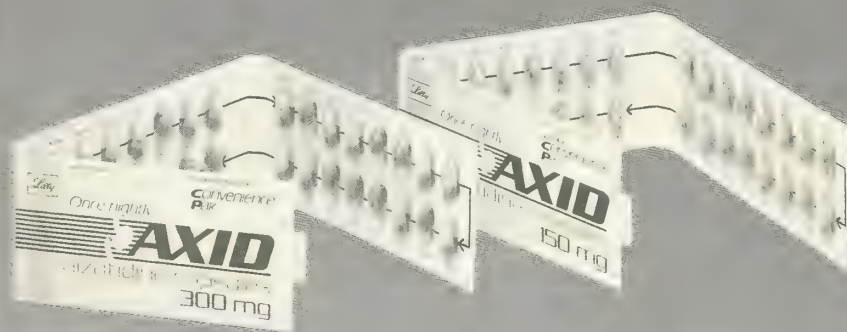
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Brief Summary

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Indications and Usage Axid is indicated for up to eight weeks for the treatment of active duodenal ulcer. In most patients, the ulcer will heal within four weeks.

Axid is indicated for maintenance therapy for duodenal ulcer patients at a reduced dosage of 150 mg b.i.d. after healing of an active duodenal ulcer. The consequences of continuous therapy with Axid for longer than one year are not known.

Contraindication Axid is contraindicated in patients with known hypersensitivity to the drug and should be used with caution in patients with hypersensitivity to other H₂-receptor antagonists.

Precautions: General – 1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency.

3. Pharmacokinetic studies in patients with hepatorenal syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver in patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests – False-positive tests for urobilinogen with Multistix[®] may occur during therapy with nizatidine.

Drug Interactions – No interactions have been observed between Axid and theophylline, cimetidine, ranitidine, nifedipine, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility – A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 60 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose female mice was within historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 350 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a two-generation, prenatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy – Teratogenic Effects – Pregnancy Category C – Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect, but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spinal bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers – Studies conducted in lactating women have shown that <0.1% of the administered oral dose of nizatidine is secreted in human milk in proportion to plasma concentrations. Caution should be exercised when administering nizatidine to a nursing mother.

Pediatric Use – Safety and effectiveness in children have not been established. **Use in Elderly Patients** – Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo. Among reported adverse events in the domestic placebo-controlled trials: sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A variety of less common events were also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic – Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients and was possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L) and, in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular – In clinical pharmacology studies, short episode of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

CNS – Rare cases of reversible mental confusion have been reported. **Endocrine** – Clinical pharmacology studies and controlled clinical trials showed no evidence of antihypertensive activity due to Axid; impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo. Rare reports of glycometastasis occurred.

Hematologic – Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H₂-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental – Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity – As with other H₂-receptor antagonists, rare cases of anaphylaxis following administration of nizatidine have been reported. Because cross-sensitivity in this class of compounds has been observed, H₂-receptor antagonists should not be administered to individuals with a history of previous hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other – Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine administration have been reported.

Overdosage: Overdoses of Axid have been reported rarely. The following is provided to serve as a guide should such an overdose be encountered. **Signs and Symptoms** – There is little clinical experience with overdoses of Axid in humans. Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous median lethal doses in the rat and mouse were 301 mg/kg and 232 mg/kg, respectively.

Treatment – To obtain up-to-date information about the treatment of overdose, a good resource is your certified regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the Physicians' Desk Reference (PDR). In managing overdose, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

If overdose occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance.

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Symptom Management in the Home-Based Terminal Cancer Patient

Edward W. Martin, MD
Walter D. Soja, MS Pharm

...Hospice care has been described as "intensive care of a different kind."¹

A common fear expressed by terminal cancer patients and their families is the fear of a painful death, preceded by days or weeks of suffering. The prevention of this scenario requires a coordinated effort on the part of the caregivers and the hospice team, working together to insure that the patient's comfort and dignity are preserved throughout the dying process. In this review, we will discuss some of the more common symptoms of terminal cancer patients and the management of these symptoms in the home.

There are some basic principles that underlie our efforts to provide comfort:

- 1) A distressing symptom in a terminally ill patient represents a medical emergency. Hospice care has been described as "intensive care of a different kind."¹ For a patient in the final days or weeks of life, 24 hours is an eternity. A symptom should therefore be managed aggressively since any delay in restoring patient comfort will severely detract from the quality time the patient and family can share.
- 2) Careful evaluation must precede any consideration of therapy. The patient is seen at home by the nurse or physician to evaluate new

symptoms or re-evaluate a change in the severity of previous symptoms. Our focus in the home concentrates on identifying readily reversible causes which may be responsible for the symptoms and then correcting or alleviating them.

- 3) The patient remains at the center of our efforts and must be provided with maximum personal control.
- 4) Enlist the support of the entire hospice team. An advantage of the hospice approach is that an interdisciplinary team is available who can approach patient problems from different perspectives. While this review will concentrate on the pharmacologic approaches to symptom management, the ongoing psychosocial support provided by the nurses, social workers, clergy and volunteers is invaluable to an effective program in the home.

Pain Management

Analgesia is a state without pain, brought about by the administration of a drug or procedure that relieves pain. Analgesia, however, is but one component of an effective pain management program. Pain is an extremely complex phenomenon, not only a function of physical injury. It also reflects the level of accompanying anxiety, the patient's expectations, and the presence of psycho-social variables. The management of pain requires a multi-disciplinary approach in order to insure successful outcome. Hospice Care of Rhode Island, or any pain management program, is committed to allow patients to function at a level of their own choosing or capability. Improving the quality of life for the patient depends on achieving a balance between effective relief of pain and the preservation of a clear sensorium. This is best achieved by allowing the patients to assume as much control of medication as they choose, while staff effectively manage or minimize medication side effects.

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Large scale statistical reviews of the incidence and severity of pain in terminal cancer are lacking. However, numerous small, specialized reviews indicate that cancer pain increases with the advancement of disease.^{3,4} Not surprisingly, studies of patients with advanced cancer suggest that 60-90 per cent of patients have substantial pain requiring some sort of pharmacological intervention.⁴ Twycross has also shown that patients with cancer have multiple causes for pain not necessarily associated with cancer.³ Foley found 20 per cent of patients required pain medications.⁵ Postoperative patients were excluded from the study. She also reported that 85 per cent of primary bone tumors, 52 per cent of breast cancers, and 45 per cent of lung cancers required some form of analgesic medications. The survey revealed that 75 percent of men and 70 per cent of women with genitourinary cancer and 80 per cent of oral cavity cancer required analgesics. Lymphomas and leukemias frequently required less analgesics than other cancers.

Before any meaningful discussion of pain can take place, an explanation of the types of pain a patient can experience is necessary. Pain can somewhat simplistically be categorized as acute, chronic, and chronic cancer pain. Acute pain is usually of short duration, where some known pathological condition exists, eg, appendicitis or abscessed tooth, and the future is generally predictable, with some form of treatment resulting in a cure. Generally there are no associated problems associated with the episode once treatment is complete. Chronic pain of a nonmalignant origin is often protracted, complex and difficult to treat. A previous injury associated with the pain may be related to the patient's discomfort. Treatment may be complicated by a psychiatric illness and/or a complex and inappropriate course of therapy. Patients with chronic cancer pain, however, differ in significant ways. They may have had a short or protracted course of discomfort.

... Pharmacological management represents but one approach to improving the quality of life of a patient with an end-stage illness.

There certainly is a definite dimension to the pathological source for their pain, even though patients can see no beginning or end to their suffering. Their future will unfold with increased pain, disfigurement, and death. Chronic cancer pain is not meaningful and it is harvested

in a losing battle fostering feelings of hopelessness, helplessness, anger, depression, and loneliness. All these factors enhance the perception of pain and ultimately worsen the extent of suffering.

Most effective hospice programs are based on an interdisciplinary approach. Pharmacological management represents but one approach to improving the quality of life of a patient with an end stage illness. However, a number of basic principles must be understood.

Assessment: Assessment is the cornerstone of a pain management program. In caring for a patient with end-stage disease, a constant review of the patient's pain state must be made. Initial doses for pain medication must be reviewed at intervals and altered to correspond to the intensity of pain. As Twycross has chided us, "Review! Review! Review!" for it is basic to cancer pain management.³

Diagnosis: In designing a more effective treatment program, it is always helpful for the clinician to know the disease with which he or she is dealing. The natural history of a disease can assist us in evaluating the onset of a new pain or the exacerbation of preexisting pain.

Individualize: Every patient is different, and while some generalizations may be made, the medication must be titrated based on his or her level of discomfort. The titration process is once again followed by review. It is also essential during titration and review to communicate with the patient about the pain and explain the reasons for episodes of pain. Although pain may still be a present and constant reminder of the underlying disease process, an explanation by the physician takes away some of the uncertainty and gives a dimension to the pain. A psychological diminishment of pain is no less important to the patient than pharmacologic agents.

Simplify and Avoid duplication: The use of more than one analgesic is unnecessary except in a few specific situations when the breakthrough of severe pain occurs in patients on controlled release morphine preparations. Patient and care-giver compliance can be adversely affected by the complexity of a drug regimen and the use of excessive numbers of drugs.

Scheduled doses: As previously stated acute pain and chronic pain are different entities and the standard doses and treatments derived from acute pain studies are irrelevant and inappropriate in the treatment of cancer pain. The goal is not only relief but also prevention. It has been determined that for many patients the total daily dose is frequently less when scheduled regimens are

compared to permissive dosing schedules.³

Anticipate patient/family medication bias: Patients and their care givers may have many misconceptions, fears, and biases about the possible deleterious effects of narcotic drugs. Clinicians must be aware of these feelings and address them with confidence and compassion.

Myths and Biases: a) "He or she will become addicted if he/she takes this medicine." Addiction is a very complex phenomenon characterized by a state of psychic and physical dependence following repeated or periodic use of the drug. Psychological dependence is associated with compulsive behavior in order to produce the psychic effects a person seeks. Physical dependence occurs when abrupt discontinuation of a drug produces a withdrawal syndrome. Physical dependence in our patients does occur to some degree but not to the extent found in drug abusers. As evidence of this fact the Boston Collaborative Drug Surveillance Program examined the records of 12,000 medical inpatients who had been given narcotic drugs. The reviewer could find only four cases which suggested a drug dependence problem.⁶ Their conclusion coincides with our experience in Hospice Care that addiction in the popular sense is a very rare phenomenon. Finally, it should be noted that patients who exhibit addictive behavior are generally found to be in poor pain control and can be "relieved of this behavior" by aggressively treating the pain.

... It is exceedingly important that we remember who is suffering.

"He really doesn't hurt that much." It is exceedingly important that we remember who is suffering. Only the patient knows the extent of his suffering. We need to listen carefully to what our patients are telling us.

"He doesn't act like he/she is in pain." Pain is not always accompanied by visible or objective signs. Adaptation occurs which can result in normal pulse, respiratory rates, and blood pressure. Behavioral adaptation can also occur resulting in little or no expression of discomfort.

"Keep your chin up. You should be able to tolerate more pain. Don't be a baby." Imposing our cultural values and expectations on a patient is inappropriate. It is important to remember that when pain is left unabated, the more difficult it will be for the patient to cope.

Tolerance: Addicted individuals require increasing amounts of narcotics to produce their

expected levels of euphoria. However, in two reviews completed at St Christopher Hospice it was shown that longer durations of treatment were associated with longer periods without dose increases.^{7,8} At the same time there was also a greater likelihood that medicine could be stopped or a dose reduced. Tolerance can never be used as a reason for withholding drugs.

... A patient's comfort and the resulting improvements in the quality of life are paramount in prescribing pain medicine.

The principles of pain management are based on the judicious use of pain medication. A patient's comfort and the resulting improvements in the quality of life are paramount in prescribing pain medicine. Patient response should guide the actions of practitioners. Drugs are meant to give relief, not to be withheld to the last possible minute.

Pharmacological Interventions

Aspirin/Non Steroidal Antiinflammatory Analgesics: Aspirin is the first step on our ladder. It is relatively safe, effective and low in cost. Aspirin is especially effective in the treatment of mild to moderate pain. It is initially used alone and is most effective in dull throbbing pain associated with inflammation. It is much less effective in pain of visceral origin. Aspirin is ineffective in sharp, stabbing pain resulting from direct stimulation of nerve endings. Aspirin's efficacy was shown in the interesting study completed by Moertel.⁹ Fifty-seven patients who had pain from inoperable disease were treated with one of nine agents. Of the drugs tested aspirin was superior. Other agents which were tested as significantly superior to placebo were mefenamic acid (250 mg), pentazocine (50 mg), acetaminophen (650 mg). Propoxyphen, promazine and ethoheptazine were found to be significantly inferior to aspirin.

Aspirin is used in combination with various drugs such as codeine, oxycodone, pentazocine, or propoxyphene. Some combinations have been found to be more effective than either drug alone; however, caution must be exercised when using combinations because undesirable dosage escalations can result.

The limitations of aspirin are well documented. Aspirin intolerance, with resultant gastritis or gastric ulceration, is not uncommon.¹⁰ Patients who are at risk should be given alternative treatment.

Aspirin use should be avoided in any patient at risk for a major hemorrhage. Aspirin inhibits cyclooxygenase release and results in the inhibition of platelet aggregation.^{11, 12}

Non-steroid anti-inflammatory, analgesic drugs (NSAID) provide a group of alternative medications which may be helpful in the patient refractory to aspirin or with limited aspirin tolerance. NSAID as a group provide no significant benefit in terms of greater pain relief, but they may prove useful to the aspirin refractory or sensitive patient. The use of any NSAID in patients with an aspirin allergy should most probably be avoided.

Several other drugs which may be helpful in relief of mild to moderate pain are acetaminophen (APAP). APAP's analgesic efficacy is similar to aspirin and is usually preferred by patients who complain of aspirin intolerance. APAP has antipyretic activity equal to aspirin but is devoid of any antiinflammatory action. Patients with hepatic insufficiency may be at risk for further injury with APAP. Combination products such as APAP and codeine or APAP and oxycodone, in our practice, have not provided the same level of relief as similar combinations with aspirin.

Codeine is an opiate with weak analgesic activity. Approximately ten per cent of a dose of codeine is metabolized to morphine and has a duration of action of two to four hours. Codeine's usefulness is limited by the increasing incidence of undesirable side effects as the dose increases. Indeed, in our practice we have seen what may in fact be a plateau effect where analgesia is not increased with increasing doses. However, with these limitations in mind, codeine is an acceptable analgesic for mild to moderate pain. When used in combination with aspirin or acetaminophen a synergistic effect occurs.⁹ Numerous fixed dose combinations are available but these combinations must be used with caution especially when dose escalation occurs.

Oxycodone is a morphine derivative which is structurally similar to codeine. Oxycodone is useful in the treatment of moderate to moderately severe pain. It is also provided as a combination product with aspirin or acetaminophen. Oxycodone is available only in oral dose forms. The side effect profile for oxycodone is similar to morphine.

Propoxyphene (Darvon and others), a synthetically derived analgesic, has questionable value as an analgesic in the treatment of cancer pain. Studies suggest that propoxyphene is not better than aspirin (650 mg) or codeine (30 mg).⁹

Its propensity to interact with other central nervous system (CNS) drugs and its ability to cause hallucinations or bizarre CNS effects limits its usefulness considerably.¹³

Pentazocine (Talwin) is an opioid derivative with both agonist and antagonist properties. It can be useful in treating moderate to moderately severe pain; however, the usefulness of all mixed agonist-antagonist drugs are limited by their ability to produce varying degrees of psychotomimetic effects such as hallucinations, bizarre dreams, and nightmares.¹⁴ These effects are more commonly seen at higher doses but debilitated patients can experience adverse effects at lower doses. Previous treatment with agonists also limits the value of subsequent agonist/antagonist therapy because of the risk of precipitating withdrawal reactions in some patients.

The opioids represent the most efficient class of analgesics currently available. In spite of the proliferation of newer agonist or mixed agonist/antagonist agents, morphine remains the standard against which all other agents are measured. It has, and continues to remain, the pharmacologic cornerstone for the treatment of severe pain. Morphine has been said to be only one sixth as potent orally when compared to parenterally administered morphine but clinical experience has revealed an oral parenteral ratio of approximately one third, indeed in some patients the ratio may be as high as one half.^{15, 16} Morphine's poor oral-parenteral ratio was thought to be due to poor absorption; however, clinical experience has proven that morphine is quite reliable when given orally, and when titrated against the level of a patient's pain, is most effective. Sublingual dose forms are now being evaluated in hope of diminishing the effects of first-pass metabolism.¹⁷

The availability of a complete line of dose forms makes morphine an extremely versatile agent. The drug is presently available in immediate release and sustained release tablets, oral liquids, suppositories of varying strengths and vials for injection. This complete line offers clinicians many options for treating patients without changing pharmacologic agents or adding new ones to supplement existing regimens.

Dosage of morphine should be based on a scheduled regimen of every four hours. Some patients who have very severe pain may require doses every three hours but this is rare. Initial doses of morphine can start as low as 5 mg, but most patients will need 10-20 mg as an initial dose. Twycross and Lack at St Christopher's Hospice examined the records of 955 patients. They

found the median dose to be 10 mg every 4 hours with a range of 2.5 mg to 180 mg.¹⁸

The inevitable question regarding scheduled or round the clock dosage is whether to interrupt the patient's sleep cycle in order to administer a dose of drug. Clinical experience has shown that many patients need not be awakened at 2:00 am or 3:00 am. There are, however, a number of patients who have significant pain on arising. These patients can be initially given 1.5 to 2.0 times their regular dose at bedtime. This alternative schedule proves helpful for many patients while alleviating the need for an early morning wake up. The use of sustained-release morphine is another alternative for treating a brittle patient. Unfortunately there will always exist a small population which will not respond to these alternative dosing techniques and will require continuous round the clock dosage.

The pharmacokinetics of morphine have not been totally clarified. Morphine is metabolized in the liver and excreted by the kidney. The extent of first-pass metabolism after oral administration is variable and not dependent on age. Bioavailability following oral use can vary from 15-65 per cent. Correlation of serum morphine concentrations to degrees of analgesia is difficult because of wide variations in patients' perception of and reaction to pain.¹⁹

Unpleasant side effects are cited sometimes as the reason for not using opiates aggressively. Many practitioners have advocated one drug over another because of an alleged reduced side effect profile, but clinical experience has shown that the opiates, when used continuously, share no advantage over one another. The more appropriate concept is to accept and anticipate the more common side effects and treat the more problematic ones aggressively.

Nausea and vomiting: Nausea and vomiting can occur not only early in treatment but can also be troublesome after an opiate regimen has been well established. Nausea and vomiting tends to be less problematic in bedridden patients but appears to pose a greater problem for women, although the reasons for this finding remain unclear.²⁰ Prophylactic treatment with phenothiazines is somewhat controversial when initiating morphine therapy. Certainly if a patient has had a prior history of nausea/vomiting then oral prochlorperazines (5-10 mg) or rectal (25 mg) every 6-8 hours should be instituted. Ambulatory patients who experience significant nausea and vomiting should be told to lie down for approximately 30-60 minutes after taking their

pain medication. It is also known that morphine can induce gastric stasis which may lead to nausea and vomiting in some patients. In these patients it is helpful to use metoclopramide to encourage gastric emptying.

... Much of the drowsiness that patients experience can be attributed not only to the drug but also to the exhaustion many patients have experienced because of inadequate pain relief.

Drowsiness: Drowsiness is usually a self-limited, transient side effect which may last approximately 3-5 days. Much of the drowsiness that patients experience can be attributed not only to the drug but also to the exhaustion many patients have experienced because of inadequate pain relief. Certainly many patients after a long struggle with severe pain will sleep for many hours once an adequate pain regimen has been started. If drowsiness persists, dosage adjustments may be necessary. Many patients prefer to tolerate some pain rather than have a clouded sensorium. Some clinicians advocate the use of low dosage central nervous system stimulants, such as methylphenidate, in the drowsy patient.

Constipation: Virtually all patients will develop constipation unless prompt and aggressive action is taken. Regularly scheduled doses of a stool softener and laxatives should be given when morphine is initiated. Bowel habits should be monitored and suppositories, enemas or manual disimpaction should be used when necessary. Mineral oil should not be used in these patients because of the potential for inducing a lipid pneumonitis if aspirated. Signs and symptoms of obstruction should be closely watched for.

Dizziness/ataxia: Elderly patients should be monitored because of the danger of a fall as a result of dizziness or ataxia. This is probably due to postural hypotension and patients should be instructed to rise from reclining positions carefully.

Hallucinations and Confusions: Hallucination and confusional symptoms may occur in some patients, especially older ones. Hallucinations, if not severe, can usually be treated by reassuring the patient no harm will ensue. Patients with more severe symptoms may require low-dose antipsychotics. The acute confusional state will usually pass in several days.

Respiratory depression: Respiratory depression has not generally been clinically important or bothersome. Mount reported his experience

... The presence of pain itself is an antagonist to the respiratory depressant effects of opiates.

in treating several hundred patients over 5½ years and found the need to use opiate antagonists on only three occasions.²¹ Walsh et al in a study of 20 patients with advanced cancer found no chronic ventilatory failure in patients receiving high doses of morphine (more than 100 mg/24 hr). This was determined by arterial blood gases and simple clinical measurements.¹⁶ Indeed, the presence of pain itself is an antagonist to the respiratory depressant effects of opiates. Morphine should obviously be used with caution in patients with chronic obstructive airway disease but it is not a reason to withhold the drug from a patient in need.

Adjuvant Analgesic Drugs: Adjuvant analgesics constitute another group of drugs which can enhance the analgesic effect of the opiates. This group includes drugs such as tricyclic antidepressants,²² phenothiazines,²³ anticonvulsants,²⁴ steroids,²⁵ antihistamines,²⁶ butyrophenones,²⁷ and amphetamines.^{28, 29} The precise mechanism of analgesic action is unknown but greater clinical interest has been given these agents in situations where morphine or other opiates produce little or only partial analgesia. Such circumstances might include the use of steroids for pain associated with nerve compression^{30, 31} or the use of carbamazepine³² or amitriptyline in post-herpetic neuralgia.³² The use of antihistamines such as hydroxyzine has been suggested to potentiate the analgesic effects of morphine.²⁶ It is important to remember that adjuvant drugs are not primary treatments but are supplements or complements to existing pharmacologic therapy.

Alternate Routes of Administration: The oral route remains the primary method for the administration of morphine, or any opiate; however a number of alternative routes exist for patients when oral medications become impossible or inappropriate to use.

Morphine suppositories can be given in a 1:1 ratio (when compared with orally administered morphine). Morphine and certain other opiates can also be given either by continuous subcutaneous or intravenous infusions.^{33, 34} These routes of administration should be used for those selected patients who can no longer achieve adequate analgesia orally or rectally. The medication is administered with the use of portable, battery-driven, infusion pumps. Intramuscular or bolus intravenous doses should be reserved for situa-

tions requiring the intermittent or occasional use of these routes of administration such as severe and sudden exacerbation of chronic pain. Epidural or intrathecal delivery of morphine has been used with success but should be reserved for those patients in whom more traditional forms of treatment have failed.^{35, 36} Only preservative-free drugs should be used for epidural or intrathecal administration. Patient-controlled analgesia (PCA) is a relatively new state of the art technology.³⁷ It involves the delivery of a predetermined amount of drug by the patient who activates a specialized infusion device. PCA has been studied and used most often in post-operative patients with great success. The role of PCA devices in patients with advanced cancer remains to be determined.

Other opiates: Morphine is the standard by which other analgesics are compared. However, there are other opiates which can be used successfully.

Hydromorphone is a morphine derivative. Its pharmacological properties and actions are quite similar to morphine. Hydromorphone is available in all dose forms and is available in a high potency injectable (10mg/ml) form which is quite beneficial when the injected fluid volumes need to be minimized.

Methodone is a synthetic narcotic derivative with an analgesic activity similar to morphine. It possesses a longer serum half-life than morphine (20-25 hr); however, the analgesic effect does not operate in parallel with the serum level.³⁸ Methadone must be administered on a 6-8 hour schedule. Older patients or patients with severe liver disease must be monitored carefully for toxicity due to drug accumulation. The extended dosing interval advantage afforded by methadone is somewhat obviated now by the availability of controlled release morphine.

Meperidine is a synthetic opiate which is routinely used in the treatment of acute and post-operative pain. Meperidine is a drug which is not particularly suited for the treatment of chronic cancer pain. The duration of action is only two to three hours and thus requires more frequent administration. The use of meperidine on a chronic basis results in the accumulation of the toxic metabolic normeperidine, which is associated with central nervous system stimulation or seizures.³⁹

Heroin or diacetylmorphine is widely used in England for cancer pain. Heroin is metabolized to acetylated morphine and then to morphine quite rapidly. It is highly soluble in water making it

attractive for patients needing large amounts of drugs in a small volume of fluid. The availability of a high potency hydromorphone injection negates much of this advantage. Studies have revealed conclusively that heroin offers no clinical advantage over morphine.^{40, 41, 42}

Brompton's solution or mixture are combination products which have been available for many years. While the contents may vary from location to location, the most common formulations include morphine, cocaine, a phenothiazine and alcohol. Practitioners have thought for years that this combination offered a clinical advantage over morphine alone. A study by Mount has revealed no clinical advantage of Brompton's mixture over morphine as a single entity product.⁴³ Most of the formulations in addition to being no more effective than morphine usually will cost the patient more money because they must be extemporaneously prepared by a pharmacist.

... The focus of any treatment should be to improve the quality of a patient's remaining time.

The treatment of chronic cancer pain is a complex undertaking. Pain is as much an emotional response as physical one. The physician has a number of alternatives in the treatment of pain such as nerve blocks, surgery, and radiation. The focus of any treatment should be to improve the quality of a patient's remaining time. Twycross described an anonymous physician who typified the misunderstanding plaguing our attempts to treat patients with endstage illness. "I try to postpone giving morphia until the very end and am best pleased if the first-dose of morphia is also the last."^{12, 44} The judicious and appropriate use of opioids in the hospice setting will only enhance the quality of a patient's remaining days and relieve a physician of much distress.

Neuropsychiatric Problems

Pain has been aggressively managed by hospice programs and is the symptom most emphasized in patient evaluation. This is certainly appropriate, for many other symptoms in the cancer patient, such as insomnia and depression, may be directly attributable to poor pain control. Most hospices now have comprehensive approaches to diagnosing and effectively treating pain in the terminally ill patient. However, other symptoms, particularly neuropsychiatric, may go unrecognized and untreated. Attention to and palliation of these symptoms can often make a profound

difference in the quality of life during the patient's final days.

A comprehensive approach to the neuropsychiatric symptoms utilizing the interdisciplinary skills of the hospice team is critical to the effective handling of these problems. In this brief review, however, only the pharmacologic aspects of management in the home setting will be discussed.

Delirium: Delirium has been reported in up to 85 per cent of terminal cancer patients during the final stages of illness.⁴⁵ Delirium, or the acute confusional state, is evidenced by a global disorder of cognition with an inability to maintain attention, and usually a disruption of the sleep/wake cycle. It is important to recall that all delirious patients are not agitated and may, in fact, be lethargic.⁴⁶ Symptoms are frequently worse at night.

In a study of hospitalized terminal cancer patients, the cause of delirium was determined in only 21 per cent.⁴⁷ The causes identified were either metabolic or pharmacologic.

1) **Hypercalcemia:** This is a frequent complication, occurring in 10-20 per cent of all cancer patients and in up to 40 per cent of certain cancers such as lung and breast.⁴⁸ In mild cases, attention to hydration and the use of steroids may correct the hypercalcemia and improve the delirium. In more severe cases, however, this may represent the terminal event, and as such, correcting the metabolic disturbance may result in unnecessary suffering and lengthening of the dying process.

2) **Hypoglycemia:** Patients with cancer and diabetes may not have altered their insulin or oral hypoglycemic dosage as their weight and oral intake declined. Adjusting, or in some cases discontinuing, these medications will prevent further episodes of hypoglycemia.

3) **Hyponatremia:** Hyponatremia may result from diuretics if the oral intake of salt has declined. Discontinuation of the diuretic and fluid restriction should restore sodium and water balance within several days.

The medications which may cause delirium are too numerous to list in this brief review. All medications being taken must be reviewed and those that are not essential to patient comfort discontinued. Drugs most frequently associated with delirium include anticholinergic drugs, digoxin, antihypertensives, narcotics and benzodiazepines, especially the longer acting agents.⁴⁹ When possible, substitute a drug with less potential for central nervous system side-effects such as sucralfate (Carafate) for cimetidine (Tagamet), or

nortriptyline (Pamelor) for amitriptyline (Elavil). Mental status may improve with discontinuation of the drug.

... Many patients with delirium can be managed with frequent reassurance and reorientation from family members.

There is no reason to withhold treatment from a severely agitated patient while searching for an underlying cause of delirium. Therapy can be started while other medications are withheld, and if needed, laboratory studies performed. Many patients with delirium can be managed with frequent reassurance and reorientation from family members. In the more agitated patients, oral haloperidol (Haldol) can be used (0.5 mg-2 mg) (or intramuscularly if needed), repeating the dose every 30-60 minutes until the agitation subsides.⁵⁰ The patient can then be managed with a twice daily oral dose. Aggressive efforts to promptly correct what may be disruptive, violent, and disturbing behavior are clearly warranted.

Insomnia

Inadequate symptom control is frequently the reason for insomnia in the terminally ill, especially poor pain control. Insuring adequate analgesia should precede pursuing other reasons for insomnia. It is also important to determine if nighttime wakefulness is a problem for the patient or for the family. The patient may not be troubled by a pattern of brief naps throughout the day, but the patient's requests for assistance during the night may be disrupting the caregiver's sleep. If other symptoms are under control and the patient complains of difficulty sleeping, a review of medications may detect the underlying problem, such as withdrawal from a short-acting benzodiazepine taken earlier in the day. The patient should be encouraged to remain as physically and mentally active as possible during the daytime hours. A short-acting benzodiazepine such as triazolam (Halcion) or temazepam (Restoril), or an antidepressant with sedating qualities such as doxepin (Senequan) can be given on a nightly basis to improve the quality and duration of sleep at night.

Anxiety

Ongoing psychosocial support of the patient and family remains the primary treatment of anxiety in terminal cancer. When medications are required, an intermediate-acting benzodiazepine

such as lorazepam (Activan) or oxazepam (Senax) can be helpful. Long-acting agents such as diazepam (Valium) or chlordiazepoxide (Librium) can have a markedly prolonged half-life in a frail, terminally ill, elderly patient. Confusion can develop as drug levels rise over days or weeks of administration. These agents are best avoided in such patients.

Seizures

Patients with a history of seizures either due to their cancer or to an unrelated problem may reach a point where they are unable to take their medications by mouth. Unable to take their anticonvulsant, their blood levels may drop and seizure may result. This will be disturbing to the patient and family and may precipitate an unwanted trip to the hospital. For such patients pentobarbital is available in suppository form and may be administered by this route for seizure control.

Depression

Depression is the most common reason for psychiatric consultation in cancer patients.⁵¹ In the terminal cancer patient, the expectations of the physician, the family and the patient may interfere with recognition and treatment of depression. Depression may be mistaken for sadness and it may be assumed that the patient should be depressed, given the circumstances. A nihilistic view that little can be offered in the way of therapy will certainly interfere with good medical care.

The diagnosis of depression can further be hampered by the frequency of vegetative signs, such as fatigue, weight loss, anorexia, and insomnia in the terminal cancer patient. An advantage to the hospice program is the input and evaluation of a number of health professionals who see the patient over a period of time. If depressed mood and anhedonia are consistently present, depression is likely and therapeutic interventions can be undertaken. An assessment regarding suicidal ideation should be part of the initial evaluation. While ongoing psychosocial support is again the cornerstone of therapy, the prompt initiation of pharmacologic intervention can often improve the quality of life for the patient's remaining days.

The side-effects profile is particularly important in selecting an antidepressant for the terminal cancer patient. Amitriptyline (Elavil) is the most anticholinergic tricyclic antidepressant and may cause orthostatic hypotension, dry mouth, blurred vision and urinary retention, symptoms

which may be poorly tolerated in the terminally ill.⁵² Use of amitriptyline is best avoided in this population. An antidepressant with sedating properties such as doxepin (Sinequan) can be used if anxiety or difficulty sleeping are also problems. While the antidepressant effect may not occur for 2-3 weeks, the sedative effects occur promptly. Nortriptyline and desipramine are the least sedating of the tricyclic antidepressants.

When fatigue and psychomotor retardation are prominent symptoms, methylphenidate (Ritalin) can be used, 10 mg at 8:00 am and noon. The effects occur promptly after the onset of therapy. Patients should be monitored closely for side effects such as insomnia and anorexia.⁵³

Gastrointestinal Symptoms

Constipation: The onset of constipation is an almost inevitable problem in terminal cancer unless steps are taken to prevent it. Numerous factors such as the predictable changes in diet and activity predispose the patient to this problem. Medications, particularly narcotics, impair bowel motility. Before starting narcotics, it is appropriate to review the patient's bowel habits and start prophylactic therapy. Docusate (Colace) and a senna preparation (Senokot) can be started when narcotics are started. If this is not adequate, a nonabsorbable sugar such as lactulose, or the less costly sorbitol, can be added.

Nausea and vomiting: The causes of nausea and vomiting in the terminal cancer patient are numerous. It is much easier to control these symptoms with the regular, rather than the occasional use of antiemetics. Combinations of medications acting at different sites can be used.⁵⁴ A phenothiazine such as prochlorperazine (Compazine) is an appropriate first step and this is available in tablet, liquid and suppository form. Metaclopramide (Reglan) or an antihistamine such as diphenhydramine (Dramamine) can be added if necessary. If pain is a problem, morphine suppositories can be used. Nasogastric suction and intravenous hydration are unlikely to improve the quality of a dying patient's final days.

Respiratory Problems

Cough: Cough is present in 30 per cent of all terminal cancer patients and in 80 per cent of patients with terminal lung cancer.⁵⁵ After excluding underlying causes which may be amenable to therapy, such as bronchospasm or congestive heart failure, an initial approach includes humidification and the use of antitussives.

Codeine and hydrocodone are commonly

available narcotic antitussives. If the patient, however, is already on morphine, the dose of morphine alone can be increased to provide adequate cough suppression. The addition of another narcotic to morphine, provides no additional antitussive action.⁵⁶ Morphine does have the advantage of being available in a suppository form, to be used when the patient is unable to take oral medications.

Dyspnea: Dyspnea can be a particularly distressing symptom for the patient with cancer. It is present in 30 per cent of all terminal cancer patients and in 65 per cent of patients with lung cancer.⁵⁷ Dyspnea may be due to a potentially reversible process such as bronchospasm or congestive heart failure, and in these cases, appropriate treatment may eliminate or reduce the dyspnea. In many cases, however, dyspnea results from the progression of the underlying illness for which no therapy is available. Oxygen may be helpful in some of these patients, but for most, the dyspnea will continue in spite of supplemental oxygen. In these patients, narcotics can provide good relief to the patient for whom each breath is an effort.⁵⁸ Treatment can begin with low doses, titrating up to control the dyspnea. Our goal is patient comfort and the risk of this effective therapy is far outweighed by the benefits to the suffering patient. Both hydrocodone and morphine can be used with good results. When the patient is unable to take medication by mouth, morphine suppositories can be used.

Death Rattle: The noise generated by uncleared secretions in the hypopharynx of the moribund patient can be distressing to the family who may feel their loved one is "choking to death." Understanding that interventions for this are done not for the patient but for the family, one can give low doses of atropine in the hours prior to death. This does not clear secretions already present, but does decrease the production of further secretions. Atropine (0.2-0.4 mg) can be given sublingually with good effect. Alternatives are glycopyrrolate which has less effect on vagal tone, and scopolamine which is available as a transdermal patch.

Summary

Comprehensive symptom management is the hallmark of good medical care of the terminally ill cancer patient. Careful attention to patient comfort and early assessment and intervention to alleviate distressing symptoms enable the patient to remain at home, and maximize the quality time which the patient and family can share.

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YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in *Rauwolfia Serpentina* (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalamic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympatholytic and mydriatic. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

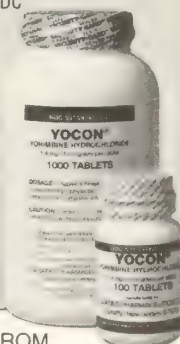
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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Reflections and Remembrances

Two brief and very personal essays written by practicing nurses in the Rhode Island community. These commentaries reflect their remembrances of the human dimensions of dying and the role of hospice in easing the accompanying burdens of anguish and grief.

I have many thoughts at a time like this, so many remembrances. It is hard to recall some things while others are still so painfully vivid. I understood that a life can change drastically from one moment to the next; but I had never thought that such changes would touch my life.

I've been a nurse for twenty-five years. Is it possible? Where did all those years go? It seems that I just graduated from Beth Israel Hospital last year, anxious to go out and try my wings. Well, I've been flying every since and I still find nursing to be rewarding and I'm happy in my chosen profession.

Now, let me think back to that special day. My Mom had complained of some abdominal pain for a few days. This was not like her so, on Friday, we went to her physician's office. Finally it was our turn and a complete examination was performed including some laboratory tests. We then went out for coffee and talked, carefully avoiding the "could-be's." On Saturday morning the doctor called saying that the blood tests were not within the normal limits and he asked that Mom be brought to the hospital for further studies.

Mom was admitted that day and there were still more tests and X-rays. The surgeon was then called and she was operated upon the next day. I worked that Sunday to help the time pass. I can remember walking out of a patient's room and seeing Mom's surgeon, a friend of mine, walking towards me. He told me that Mom had cancer of the gall-bladder with liver metastases. I didn't hear anything else after that. I went to her hospital room, sat down, and cried. Sometimes a numbness protects us and by the time Mom had been returned from the recovery room, I had managed to interrupt the tears and to control myself.

That evening Mom's doctor shared the grim news with her, the news that she had so dreaded. Her first response was to cry. In the quiet of a

hospital room we then shared our once silent thoughts.

The next few days are blurred in memory. My brother flew in from California and there were many family meetings to decide what next to do. My immediate family, my husband and two teenage daughters, met and we agreed that Mom would stay in our home after discharge. Mom went along with our plans "until she got stronger."

We brought Mom's bed to our home and set it up in the living room, now her room. I remember the relieved look on her face when she walked through the front door. She was glad to be home.

The next step was to call Hospice Care to help us to make an unbearable situation somewhat tolerable. They assured us that we could reach one of their nurses at any time and that the inevitable pain would be controlled.

In the next few weeks we shared so much during the limited, precious time allotted to us. Mom and I had always been close to each other and freely shared and expressed our feelings, but knowing that time was running out, made these days more special. How could we put a lifetime of living in but a few weeks of dying? Each day we saw Mom slipping away from us. How easy it was for me to care for my patients, but how difficult the easiest of nursing tasks became for me as a daughter. I sought and found much needed support from my family and will always be grateful for their love, patience and understanding.

Our last night together was spent in talking. I told my Mom exactly what I thought and how lucky I felt to have had her as my mother. We had never gone through the difficulties that some mothers and daughters experience. Our closeness which made this final night easier also made the final separation almost unbearable. It is so difficult to let go.

My Mom died peacefully in our home, in her own bed, with her three children by her side and with her grandchildren and friends close by. She had given us the gift of life and now she is gone.

Judith Lynn Gordon, RN
Admissions Director,
Hospice Care of Rhode Island



The room is dim, music faintly heard throughout the house. The curtains part to allow the cool summer breeze to soothe this caregiver's task. Her face is tranquil. The skin is soft, relaxed. Family members walk in and walk out. It is not clear even to themselves why they have drifted in. Yet, they pause and smile or cry and observe this holy sacrament. It is difficult to imagine that this lifeless body endured the ultimate battle this past evening. It seems so long ago. . . .

The front door is open. There is no need to knock tonight. The living room is empty. One moves slowly through the house searching for signs of life. Muffled voices are heard beyond a closed door. As the door is pushed forward, all eyes turn in anticipation. The woman lying in bed slowly closes her eyes. The energy is gone that once held them open. Her lips are parched despite the constant nurturing of her attentive daughter. Her breathing, described as "labored" at this point, is urged on by all in the room. She grasps a hand and nods that she knows we are there — her coaches — wiping her brow, rubbing her back, easing her pain. She has fought all evening awaiting the arrival of her son. She is frequently assured that he will be there soon.

We are in her bedroom, her own bed pushed to the side, the hospital bed in the center. Her bureau stands where it has always stood. Her jewelry box, her comb and brush and a photograph adorn its surface. The photograph is of a young bride: hopeful, healthy. It is such a contrast to view the bride tonight: prominent cheekbones, sunken eyes, swollen abdomen, gasping for life. Such a struggle this has been. The initial symptoms, the diagnosis, the rigorous treatment, and finally the decision to come home to die. Everyone in this room participated in all these decisions along with the absent son. So much time has passed, so little time left.

A neighbor drops in, bringing dinner for the family. She peers into the bedroom and sees her

friend of twenty years. Shouldn't she be in the hospital? Where is the doctor? The daughter asks if she would like to sit by the bed and say good-bye. She shakes her head, tears in her eyes, not understanding. She will be next door if she is needed. The daughter hugs her. The patient smiles.

Her husband caresses her face, brushing her cheek with a soft kiss. "He will be here soon, love." "I know," she replies. All look on, deep in thought. All have their private memories playing and replaying in their own minds. She is wife, mother, daughter-in-law, aunt, cousin, daughter, friend; so important to so many. It is a privilege to participate in this personal journey, this time of growth. To see a mother say goodbye to each of her children over a six week period is quite an experience. Not all are as brave as she, not all are as determined as she. Each child has spent time alone with their mother. There is so much to learn. Her husband is there all of the time. He lies on their bed all of the time prepared to fulfill every need. They have had frequent good-byes these past six weeks. They have laughed together and they have cried together. Tonight they are fighting together for time. The plane should be arriving at 10:50 pm. She coughs — we all respond: one lifts her, one turns her, one massages her back, one suction her. The fever is raging, the sweat pours down her face. Just one more hour. Please, Lord.

Music is playing softly. Her parents arrive, but remain in the living room. Her father sobs, doubled over in the oversize wing chair. He cannot bear to see his baby. Is she comfortable? How much longer? The patient responds to the soft music, her face relaxing. She scans the room, stopping at familiar eyes, the picture of her children, her husband's hand. It is clearly more difficult for her to breathe now. She squeezes his hand and we breathe along with her. The phone rings: they are on their way home. A sigh of relief. She nods, smiles and continues her arduous task.

It is peaceful in this room. Much work has been done and all are feeling a strength from this. Everyone surrounds the bed, touching, holding, waiting. The front door is opened. "I'm home, Mom." She nods, she smiles, she holds, she cries. It is time.

Mary Kate Grzebien Carpenter, RN
Patient Care Coordinator
Hospice Care of Rhode Island

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1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.

2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.

3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics; see **WARNINGS**.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS**, **WARNINGS**, and **OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS**); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 mEq/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.

3. Correction of acidosis, if present, with intravenous sodium bicarbonate.

4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

Fifty Years Ago (JULY 1939)

The Presidential Address, entitled "The Obvious and the Platitudinous," was delivered by Edward S. Brackett, MD, president of the Rhode Island Medical Society from 1938-1939. He describes the change in the doctor-patient relationship due to increased specialization and involvement by the state. "More and more the practice of medicine will be dominated by organized forces outside of the profession. . . . the rise of specialism, the concentration of hospitals and clinics and the ever increasing tendency to shift the responsibility for the care of the sick to the state, have already and will continue to raise problems that must be solved. . . . In the old days, when the individual doctor treated directly with his patient and his fellow practitioner, a strict adherence to the golden rule was all that was necessary for peace, justice and happiness in the cult of the healing art. . . . But times have changed. No longer can we practice medicine, shaping our relations with our patients and our fellow practitioners with no other guide than allegiance to our Hypocratic oath. No longer is the state content to leave us to our own devices, trusting to our interest in the public welfare and our devotion to our patients."

The lead article entitled, "The Treatment of Pneumococcus Pneumonia with Sulfapyridine," is authored by J.E. Greenstein, MD and Raymond E. Stevens, MD. The authors note, "Not since the time of Ehrlich has chemotherapy received such a stimulus as when Dogmak in 1935 announced a new chemotherapeutic agent. This agent he found effective in the treatment of experimental streptococcal infections in mice and also moderately effective against pneumococcal

infections, particularly those due to type III. His original preparation was an azo dye called Streptozon or Prontosil. Other workers found that the activity of the drug was due to the part containing the $O=S=O$ radical. This fraction, which was separated, was called Sulfanilamide. Although our cases showed relatively few toxic manifestations referable to the medication, nevertheless we feel that this drug, while having a decided beneficial effect in the treatment of pneumonia, should not be given indiscriminately or without regard to the possible toxic manifestations. And in conclusion, "Sulfapyridine is an effective therapeutic drug in the treatment of pneumococcus pneumonia, causing a decrease in the mortality and morbidity of this disease and shortening the convalescent period. It appears to be a relatively safe therapeutic agent, but should be used with caution with regard to its toxic possibilities."

Twenty-five Years Ago (JULY 1964)

The lead article entitled "The Expansion of Knowledge" is authored by Barnaby C. Keeney, PhD, then President of Brown University, and is an address delivered to the Rhode Island Medical Society on its 153rd anniversary. Dr Keeney reflects on the increase of information available and the need to continue one's education or risk obsolescence. "Yet . . . a very high percentage of the information bearing on the problem will not be available and cannot be used, for there is as yet no way quickly to collect and collate it — or even to get access to it. This situation will change radically, perhaps in the next decade. It is already theoretically possible to pour the contents of all the libraries in the world into a machine and

instantaneously to retrieve all the information that bears upon any particular subject. It is not yet mechanically possible or economically feasible to do so, nor have we devised an intellectual framework within which to arrange the information. When these things are effected, as they are likely to be within our time, the use of knowledge will become an even more powerful instrument than it is today."

Another paper entitled "Some Present Day Concepts of the Therapy of Diseases of the Thyroid Gland" is written by Milton W. Hamolsky, MD, then Physician-in-Chief at Rhode Island Hospital.

The lead editorial addresses the controversy over controlling hospital costs through elimination of unused beds, with the premise that current hospital expansion occurs unnecessarily due to lack of central planning. The author states, "We submit that any attempt to keep down hospital utilization by limiting the number of hospital beds would be unwise, unwarranted, and a disservice to the community. We take serious exceptions to any effort to control utilization by enforcing a built-in bed shortage. Additional hospital construction should be hailed and not discouraged."

Another editorial reports on an increase in syphilis cases in Rhode Island. Attempts to combat this disease meet little success due to lack of public funds for treatment, stricter regulations on the use of penicillin, and lack of epidemiological data. "The key to the conquest of syphilis is treatment of the undiagnosed early infectious case."

Vital statistics from the Health Department for July, 1964 show an overall mortality rate of 10.8/1000, an infant mortality rate of 24.3/1000, with a birth rate of 21.0/1000. An increase in death rates was reflected for congenital malformations, diabetes mellitus, influenza/pneumonia, and heart disease.

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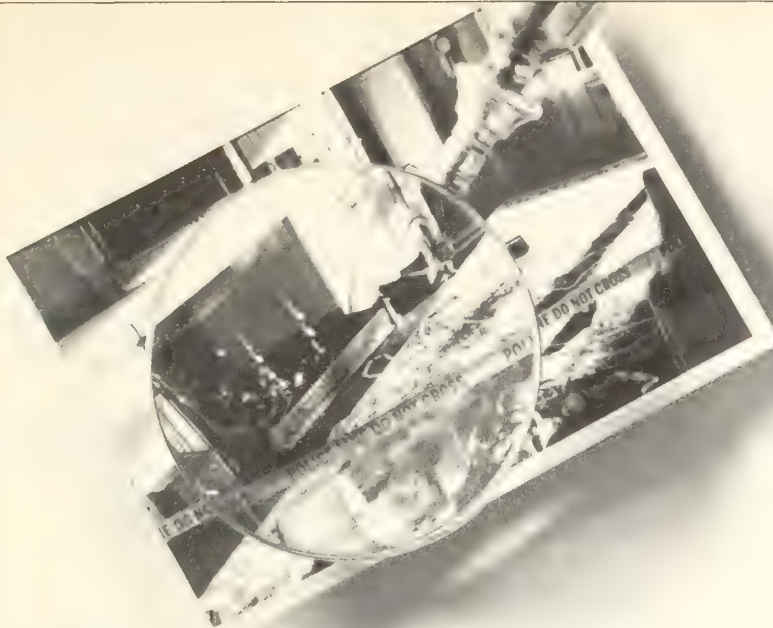
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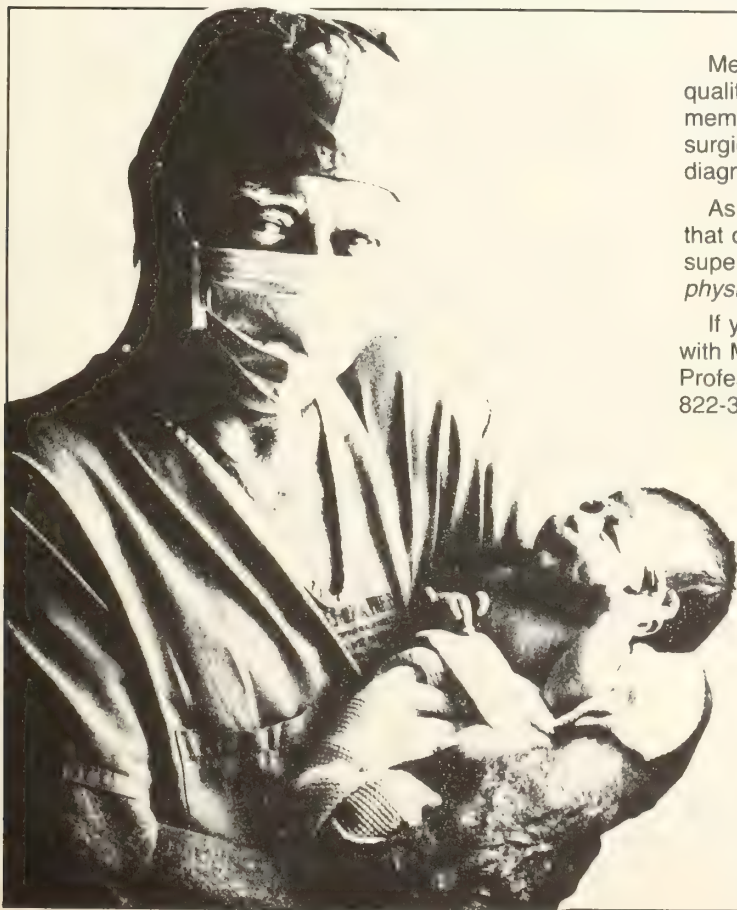
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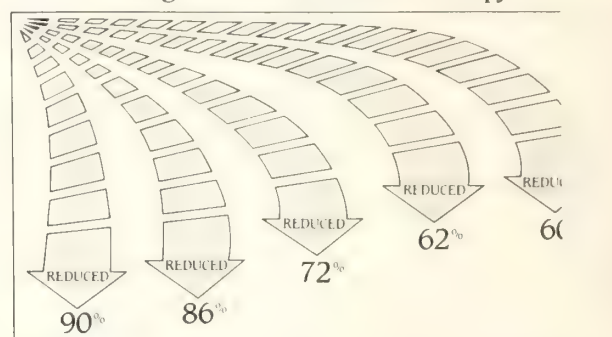
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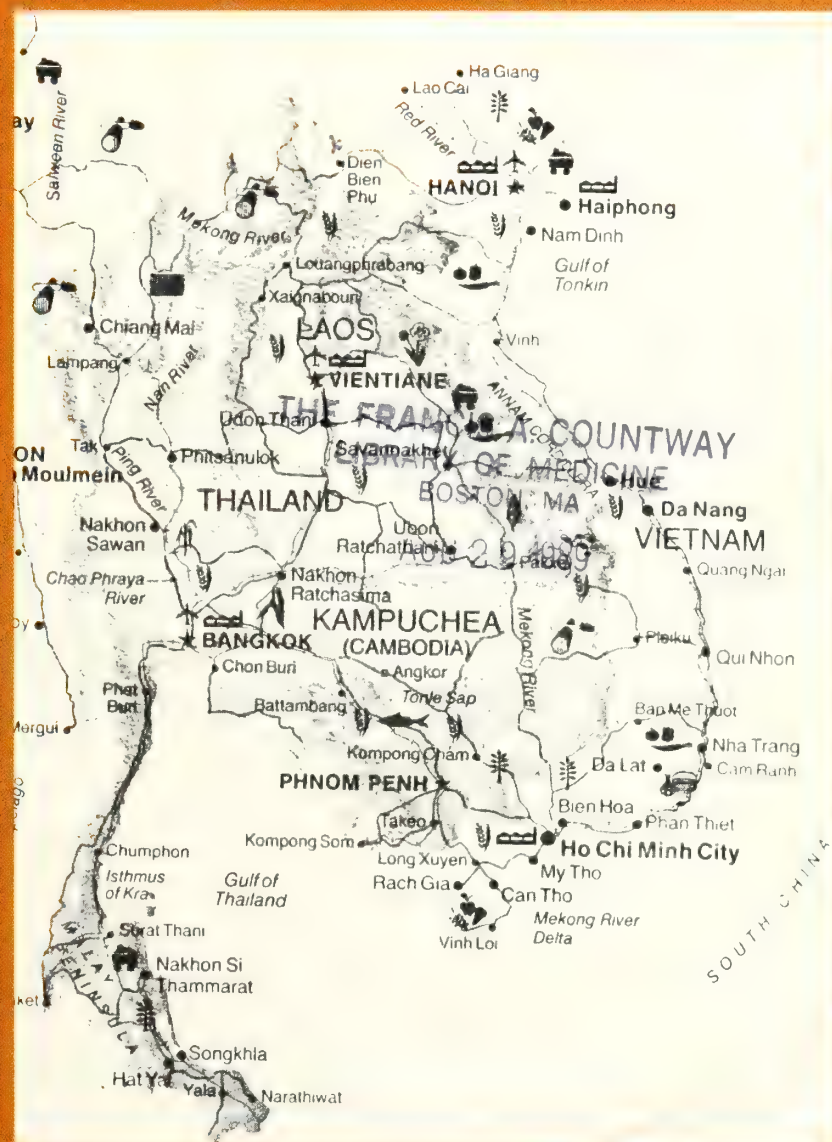
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RHODE ISLAND MEDICAL JOURNAL

August 1989

Volume 72, Number 8



*Health Concerns of
Southeast Asian Refugees
in
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There must be a good reason why



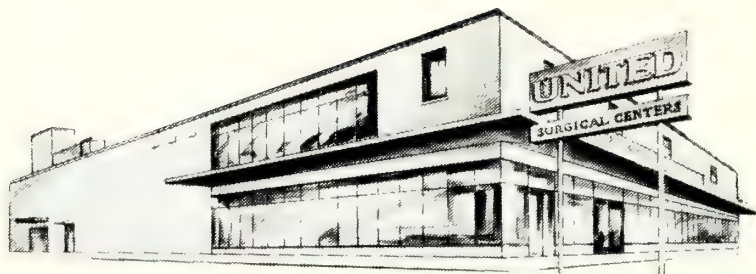
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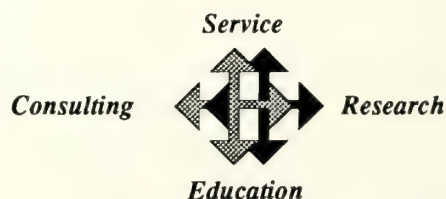
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Cover: *Map of Southeast Asia, homeland for Cambodian, Hmong, Laotian, and Vietnamese refugees, many of whom have resettled in Rhode Island since 1976. Reprinted from National Geographic Picture Atlas of Our World, National Geographic Society, Washington, DC, 1980: 180. Courtesy of Warwick Public Library, Warwick, RI.*

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Guidelines:

- 1) The original and one copy must be submitted by January 1, 1990 to Secretary, Caleb Fisk Fund, Rhode Island Medical Society, 106 Francis Street, Providence, Rhode Island 02903.**
- 2) All papers must be double-spaced and should not exceed 10,000 words.**
- 3) The Trustees reserve the right to award one or more prizes.**
- 4) The award recipient(s) must transfer copyright privileges to the Trustees of the Caleb Fiske Fund of the Rhode Island Medical Society. The paper will be considered for publication in the *Rhode Island Medical Journal*, subject to review by the Editorial Board.**
- 5) The award recipient(s) will be presented with the prize amount, to be determined by the Board of Trustees of the Caleb Fiske Fund, at the Annual Meeting of the Rhode Island Medical Society to be held in May, 1990.**

EDITORIAL

Give Us Your Tired, Your Poor, Your Huddled Masses

Since 1976, some 14,000 Southeast Asians have sought haven in Rhode Island. They are part of a larger wave of over one million displaced Cambodians, Laotians, Hmong and Vietnamese who fled their native Asian nations to seek citizenship in the United States. The Rhode Island Southeast Asian Refugee Health Screening Program estimates that there are 6,660 Cambodians, 2,394 Hmong, 4,570 Laotians, and 500 Vietnamese currently in this state.

Rhode Island continues to welcome new refugee arrivals but in somewhat smaller numbers. During the past two years, for example, 608 immigrants have been documented as new residents of Rhode Island. The ethnic origins of these new arrivals are as follows: Laotian, 268; Cambodian, 65; Hmong, 77; Vietnamese, 29; Thai, 30; European, 130; other, 9. Southeast Asians, who comprise 77 per cent of these recent arrivals, still dominate the ranks of new immigrants to Rhode Island. They come largely from other states in a secondary immigration, but some have arrived directly from overseas refugee centers situated in Thailand and other Asian countries where they had been provided with temporary housing. Theirs has been a traumatic transit from their native villages, some crossing hostile borders by land, and others traversing the treacherous waters of South China Sea in unseaworthy craft, before finding some marginal shelter in the intermediate resettlement centers of Asia. There they remained for months or years, inactive, and with little opportunity for developing language or occupational skills, until finally the chance for resettlement in the United States materialized, and the beginnings of a new and independent life became possible.

Where Are They From?

Laos, a land-locked nation, is almost equal in size to the combined areas of New York and New England. Its population density, however, is low (40.5 persons per square mile). Neighboring Cambodia, about the size of Missouri, borders on the Gulf of Siam, and is somewhat more populated (91.6 persons per square mile). New England, on the other hand, has a density of 201 persons per square mile (and Rhode Island, 918 persons per square mile).

What Are Their Demographic Characteristics?

Most of the Southeast Asian immigrants are quite young, with a median age of 20 years. Their number of elderly is small, perhaps about two to three per cent. The majority derive from rural villages, and bring with them virtually no technical skills; most are poorly educated, frequently illiterate. The two larger groups, Cambodian and Laotian, are for the most part Theravada Buddhists, while the Hmong, from the mountainous regions of Laos, are animists.

Where in Rhode Island Have They Settled?

At the moment the overwhelming majority are clustered in the poorer Providence neighborhoods in the West End, Elmwood and South Providence districts (82.1 per cent); northern Rhode Island, largely Woonsocket (12.9 per cent); and the Cranston/Johnston region (3.4 per cent). Their housing is typically dilapidated, old and with walls bearing decades-old, peeling, leaded house-paint. Lead poisoning affecting the Southeast Asian children becomes a predictable public health concern. The article by Simon, Zimmerman and O'Conner in this issue of the *Journal*,

provides us with some of the epidemiologic dimensions of the problem.

Are There Serious Health Problems in this Population?

Health problems of Rhode Island's Southeast Asian refugees are indeed substantial. Surveys indicate that at least 80 per cent have some medical problem requiring active professional intervention. These organic problems include parasitic infections, hepatitis B, tuberculosis and various sexually transmitted diseases. An article in the current issue of the *Journal* by Chow and Krumholtz emphasizes the magnitude of medical problems, particularly those of infectious origin, in this population of refugees.

Rudimentary medical needs can be met with but minimal communication between patient and physician. The rendering of psychiatric care, on the other hand, requires the services of bilingual mental health workers of which there are very few. Yet another obstacle is the deep reluctance of Southeast Asians to seek psychiatric assistance. Their cultures attach no credence to the western etiologic concepts of mental disease, and when confronted with mental disease, they will resort to herbal medicines and employ shamans and Buddhist monks rather than the secular "talk treatment" of the western nations. About 150 Southeast Asians are now being served by the mental health clinics of the state, while the true need is estimated to be over 1,000.

Three mental health centers, each with bilingual translators and health workers, now offer effective psychiatric and counselling assistance to Southeast Asians:

Northern Rhode Island Community
Mental Health Center
58 Hamlet Avenue
Woonsocket, Rhode Island
765-7171, David Yuells

Providence Center
520 Hope Street
Providence, Rhode Island
274-2500, Loeun Ros

St Joseph Hospital Southeast Asian
Support Center
21 Peace Street
South Providence, Rhode Island
456-4422, Diane Piezi

The measure of risk for mental illness among the Southeast Asian refugees is considerable. Numerous studies, including those conducted in

Rhode Island by Chow, Krumholtz and Landau, in this issue of the *Journal*, have concluded that more than 76 per cent of Southeast Asians living in the United States suffer from some profound degree of emotional distress or depression.

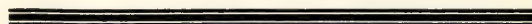
The Refugee Services Subcommittee of the Governor's Council on Mental Health has recommended: "For the foreseeable future Rhode Island's Southeast Asian communities will require specialized mental health services if their needs in this area are to be adequately met. "Mainstreaming" of Southeast Asians, that is, offering them more-or-less unmodified versions of mental health services available to the general public (with possibly the addition of interpreter assistance) is not currently an appropriate service option. The recent history of these peoples have been too traumatic, their cultures are too different, and their concepts regarding mental health and illness are too much at odds with Western notions to allow the needs of these communities to be smoothly accommodated by our existing service structures and therapeutic approaches."¹

The transition from refugee status to productive citizenship is typically painful and prolonged. But Rhode Island and Providence Plantations have historically been enriched by successive pulses of immigrants seeking haven here. Even Roger Williams was a refugee.

Reference

- 1 "Meeting the Mental Health Needs of Rhode Island's Southeast Asian Communities," Report by the Refugee Services Subcommittee of the Governor's Council on Mental Health, September, 1988.

Stanley M. Aronson, MD



Message to Rhode Island Physicians

During this past year at least two Rhode Island physicians died as a result of suicide. Each year at least one physician in Rhode Island can be expected to commit suicide (based on national physician suicide rates). While male physicians commit suicide at a rate which approximates the age-matched general population, female physicians manifest a rate which is three times that of the general population. It is likely that many more physicians kill themselves than we know. The cause of death is often recorded as accidental or due to illness by a friendly colleague wishing to spare the family the added grief of public notice of suicide. Occasionally we are made aware of these tragedies when they become front page news. More often they are not publicized. A physician suicide (by intravenous drugs) in Rhode Island within the last year was unknown to all but the closest family and associates.

... We believe that with proper education the healing profession should be able to make progress in the treatment of suicide as well as education.

Whereas members of the general population often make suicide attempts or gestures which do not result in death, physicians are remarkably efficient, in that 62 per cent of physician suicide attempts result in death.

There are many parallels between our attitude toward suicide and that toward addiction. Not too long ago physicians took a defeatist attitude toward addiction in themselves and their colleagues. Now we know that recovery is possible in 85-90 per cent of addicted physicians when treated in special programs. In the universal grief in our community over a recent tragedy we have also detected a hopelessness about the issue of suicide which is very similar to that encountered 11 years ago about addiction. We believe that with proper education the healing profession should be able to make progress in the treatment of suicide as well as addiction.

The American Medical Association and the

American Psychiatric Association have published the results of a joint study on physician suicide (*JAMA* 257:2949-2953, 1987). By understanding some of the characteristics of a potentially suicidal physician and by having a mechanism in place to bring professional help to the troubled physician we should be able to attack this problem. According to the AMA-APA study, characteristics of suicidal physicians include:

- Self prescription of a psychoactive drug*
- Previous suicide attempts*
- Talk about suicide*
- Financial loss*
- Drug and/or alcohol dependence
- Personal or professional loss
- Family history of chemical dependence or mental illness
- Depression
- Receives little emotional support from family, colleagues and friends
- Gives little emotional support to family, colleagues and friends
- History of psychiatric hospitalization
- Chronic mental illness
- Chronic physical illness
- Critical attitude toward him/herself and others

Characteristics marked with an asterisk (*) denote a high probability of suicide. The presence of any of these starred factors in combination with a history of one or more previous suicide attempts portends an extremely high probability of suicide.

What does all this mean? It means that we have enough data to be able to recognize changes in our colleagues which might be indicative of potential suicide.

What should you do if such signs should be apparent in a physician? It may be possible to intervene on a personal basis. The object of such an intervention should be to get the physician into treatment with a competent psychiatrist. Given the closeness of the medical community in Rhode Island, the psychiatrist should be from a different hospital or practice area than the suicidal physician. This will facilitate confidentiality and make ob-

jective treatment easier for both the treating and the patient physician.

What should you do if your colleague is unreceptive to your intervention or if you feel uncomfortable about confrontation? Such a situation might occur if the potentially suicidal physician were a close friend or were in a position of authority. The Rhode Island Medical Society Impaired Physician Committee will intervene in any case in which there is a threat of potential suicide. Members of the committee include psychiatrists and others with experience in addictions, depression and other behavioral disorders. The committee has intervened in over 125 cases in Rhode Island and has established protocols for these confrontations. Sympathetic referral for treatment is the objective. The committee itself does not provide treatment. Patients are referred to appropriate specialists for confidential treatment. The committee does follow up to make sure the physician actually starts and continues the recommended therapy. We accept referrals from any source including physicians, other health professionals, families, etc.

What should you do if you have disturbing suicidal thoughts? Call the committee! We will help you contact a psychiatrist. Absolute confidentiality is guaranteed.

Treatment is not always successful in any disease, but it has no chance at all if it is not instituted. Please be alert for the signs of potential suicide in your colleagues. If you feel uncomfortable about acting on your suspicions call the Rhode Island Medical Society at 331-3207 and a member of the Impaired Physician Committee will call you back for a confidential discussion. Talking to a troubled physician is a sign of caring and has no side effects. It may save a life!

Donald R. Coustan, MD
President, RIMS

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Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

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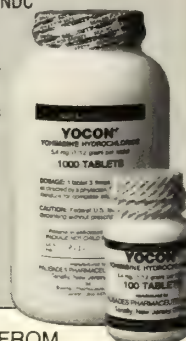
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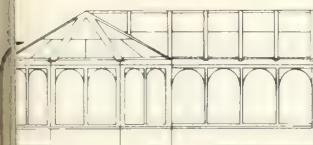
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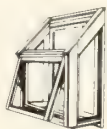
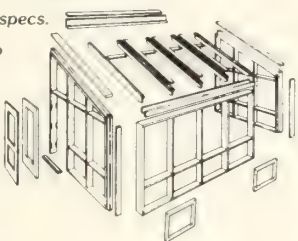
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Health Screening of a RI Cambodian Refugee Population

Robert Tao-Ping Chow, MD
Seba Krumholtz, MD

Our sample population has lived in the United States for about three years, and yet their disease prevalences have not shown any significant changes from the disease prevalences amongst Cambodian refugees to the United States obtained four to seven years prior to this study. We recommend, therefore, a continued surveillance and vigilance for communicable diseases in this population.

It has been estimated that approximately 800,000 refugees from Southeast Asia have immigrated to the United States since 1975.¹ Roughly 10,000 to 13,000 refugees now reside in Rhode Island with the figure gradually increasing due to shifting economic factors in the United States. From the public health standpoint, this population presents a significant and unique challenge to the Rhode Island medical community. Though many authors have studied specific disease prevalences,²⁻¹⁰ the information that has accrued are drawn from small geographically and ethnically isolated sample groups. In any one urban area, it has been shown that there is significant variation in prevalence rates among the different ethnic groups.² Though inferences may be drawn for the Rhode Island group, specific data and its fluctuations in time are not readily available.

From 1982 to 1983, Bicho and Keenlyside¹¹

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reviewed the health problems among 249 primary immigrants and 40 secondary immigrants screened at the clinics of the Providence Ambulatory Health Care Foundation. In general, they found a young population of immigrants who were basically healthy and free of significant communicable disease. These results contrast sharply with other data obtained nationally. Our study attempts to verify this conclusion and update the data for the Rhode Island Cambodian population. We hope to establish local disease prevalences and ascertain trends over time.

Methods

This retrospective study was performed at the Central Health Center, a Providence Ambulatory Health Care Foundation non-profit community-based health center in Providence, Rhode Island. The majority of the patients there are of Cambodian descent, and health care providers are assisted by a bicultural staff. The site provides primary care in internal medicine, pediatrics, obstetrics, gynecology, and nutrition counselling. Patient referral sources include family members, sponsors, friends, and churches. In addition, this clinic represents a site for screening of new Cambodian immigrants.

A chart review was performed of 113 consecutive adult Cambodian patients seen by the authors at the internal medicine clinic of Central Health Center from January 1, 1986 to December 31, 1986. Demographic data on age, sex, marital status, years in the United States at the time of screening, proficiency in English, presence of symptoms, living situation, tobacco use, and alcohol use were recorded. Following the recommendations of others,^{12, 13} the Mantoux skin test for tuberculosis (0.1 cc subcutaneously), hepatitis B surface antigen assay, complete blood count, VDRL test for syphilis (with all positive tests confirmed by FTA-ABS), and stool for parasite analysis were requested. Data were coded and processed using the MacStats Statistical

Package. Statistical significance was tested by performing a Chi Square analysis, with 0.05 set as the level of significance. When either the independent or dependent variable were non-integers (eg, length of time in the United States), a correlation coefficient was calculated.

Results

Table 1 presents the demographic data of the sample. Though the patients were relatively young, it was difficult to compare this to age distributions for the Rhode Island population as a whole or the sample used by Bicho and Keenlyside¹¹ because the pediatric population has been excluded from our sample.

The results of disease screening for this population are shown in Table 2. Also shown are the results obtained by Bicho and Keenlyside¹¹ upon screening 249 primary immigrants and 40 secondary immigrants during a one year period from

April 1, 1982 to March 31, 1983.

Several demographic correlations were obtained. The increased proficiency in English portended greater likelihood of employment ($p < .01$, $\chi^2 = 97.6$, $DF = 4$.) Proficiency in English correlated with the number of years in the United States (correlation coefficient = 0.40). Men were more likely to be employed ($p = .011$), smoke tobacco ($p < .01$, $\chi^2 = 13.2$, $DF = 1$), and drink alcohol ($p < .01$, $\chi^2 = 7.07$, $DF = 1$). Tobacco use also correlated positively with the number of years spent in the United States (correlation coefficient = 0.30).

Tuberculosis

More than half of the patients showed a positive skin reaction ($>10\text{mm}$) upon initial testing. These patients were referred to the Roger Williams General Hospital Tuberculosis Clinic for further evaluation and therapy. The presence of a positive PPD test correlated with tobacco use ($p = 0.01$, $\chi^2 = 6.38$, $DF = 1$) and male gender ($p = 0.04$, $\chi^2 = 3.91$, $DF = 1$). Catanzaro and Moser² found 57 per cent positive tests among Cambodian patients in San Diego in 1981, while Barry *et al*⁷ had 40 per cent positive results at a clinic in New Haven, Connecticut in 1979. Erickson and Hoang⁶ in 1979 noted 62 per cent positive PPD tests among 194 adult Cambodian patients in Hartford, Connecticut, while Judson *et al*¹⁰ found 50 per cent positive reactions among Cambodian refugees in Denver, Colorado in 1982.

Hepatitis B

A positive Hepatitis B surface antigen test was found in 7.8 per cent of this sample. A positive test correlated with presence of parasites as noted through routine stool sampling ($p = 0.02$, $\chi^2 = 5.82$, $DF = 1$). Catanzaro and Moser² found 14 per cent prevalence of Hepatitis B surface antigen in their sample, while Barry *et al*⁷ and Judson *et al*¹⁰ noted 16 per cent and 15 per cent test positivity respectively.

Intestinal Parasites

The prevalence of intestinal parasites was 68 per cent. Hookworm was the most common organism, but *Entamoeba histolytica*, giardia, and ascaris were also found. The presence of parasites did not correlate with eosinophilia ($p = 0.31$, $\chi^2 = 1$, $DF = 1$). Parasitic infestation also did not correlate with the number of years in the United States (correlation coefficient = 0.067). Hoffman *et al*³ found a 62 per cent prevalence among Cambodian patients screened at two primary care

Table 1. Demographic Information on 113 Adult Cambodian Patients Seen at Central Health Center, Providence, Rhode Island, 1986

Age Mean = 39 years (range 19-75 years)	
Sex	
Male	49
Female	64
Total	113
Marital Status	
Single	15
Married	74
Widowed	18
Divorced	6
Mean Duration in the United States, 2.8 years (range, 2 mon.-10 years)	
Living Status	
Alone	1
With spouse and/or children	86
With parents and/or siblings	10
With friends	4
N/A	12
Use of English language	
Rudimentary: Yes, no, hello, etc.	75
Responds to simple commands, but requires interpreter	23
Communicates independently in English	14
N/A	1
Employment	
Employed	13
Unemployed	89
Student	9
Admits to use of alcohol	
Yes	19
No	78
N/A	16
Admits to use of tobacco, including chewing	
Yes	42
No	57
N/A	14

Table 2. Prevalence of Diseases among 113 Adult Patients in 1986 as Compared to 295 Southeast Asian Refugees Screened in 1984¹¹

	113 Adult Cambodian Patients Screened in 1986			295 Southeast Asian Refugees Screened in 1984		
	Number Screened	Number Positive	Prevalence	Number Screened	Number Positive	Prevalence
PPD test	103	63	61%	295	62	21%
Hepatitis B Surface Antigen test	96	7	7.8%	292	14	4.8%
Stool for Parasites	91	62	68%	292	73	25%
Anemia*	107	28	26%	235	8	3.4%
VDRL test	89	21	24%	222	6	2.7%

*For males, less than 14 gm %; for females less than 12 gm %.

clinics in San Diego, California in 1978, while Barry *et al*⁷ found a rate of 59 per cent. Catanzaro and Moser² found 61 per cent prevalence of parasitic infestation, while Erickson and Hoang⁶ found 65 per cent.

Anemia

Twenty-six per cent of patients screened were found to have anemia, based upon a low hemoglobin count (less than 14 gm per cent for male and less than 12 gm per cent for female patients). Catanzaro and Moser² found a prevalence of 37 per cent. Though they found a positive correlation between anemia and presence of parasites, this was not borne out in our population ($p=0.62$, $\chi^2=.24$, $DF=1$). Twenty per cent of Cambodian patients studied by Judson *et al*¹⁰ were found to be anemic. Erickson and Hoang⁶ found 16 per cent had anemia, but their thresholds for anemia were lower than those used in other studies (hemoglobin less than 13 gm per cent for males, less than 11 gm percent for females). Sutherland *et al*,⁹ using the criteria of hemoglobin less than 12 gm percent for males and less than 11 gm percent for females, found 12 percent of 426 Cambodian patients to be anemic in Rochester, Minnesota, from 1975 to 1981. Craft *et al*¹⁴ identified 18 per cent anemia among 142 refugees in New Haven, Connecticut, in 1980.

Serologic Tests for Syphilis

Positive VDRL with positive confirmatory FTA-ABS were found in 24 per cent of this population. None were symptomatic at the time of screening. No association was demonstrated with any other variable. Catanzaro and Moser² found 19 per cent of their Cambodian population had positive serologic reactions for syphilis.

Comments

In this study, the prevalences of tuberculous skin

reactivity, positive serologic tests for Hepatitis B, intestinal parasites, positive serologic tests for syphilis, and anemia were determined in an unselected group of Cambodian patients who visited an adult primary care clinic in Providence, Rhode Island during 1986. The prevalence of these diseases amongst Cambodians agreed generally with the results of previous authors around the United States but contrasted sharply with the results of the Rhode Island study by Bicho and Keenlyside.¹¹ Because their Southeast Asian refugee patients were only 50 per cent of Cambodian descent and 34 per cent younger than eleven years old, the sample populations may not be comparable. Nonetheless, it is difficult to reconcile the greater than three-fold differences in the disease prevalences and the reassurances that were implied by their study. Our data suggests that the disease prevalences among the Cambodian population in Rhode Island are similar to national averages obtained from 1979 to 1982.

Tests for tuberculosis, syphilis, and intestinal parasitism remain high.

Evaluation of the population demographics reveals that men are more likely than women to be employed, admit to using tobacco, and drink alcohol. Tobacco use correlated with the presence of a positive PPD test, and increased with number of years spent in the United States. Proficiency of English also correlated with time spent in the United States, and also the greater likelihood of being employed. It is possible that these factors are determined in some manner by the family structure of the Cambodian family and its assimilation into western culture. Further anthropological and sociological analyses, however, would be necessary to clarify the causative factors.

The rate of Bacille Calmette Guérin (BCG) vaccination in native Cambodia, and in our sample population, is unknown. The patients with positive skin tests were referred to a specialized clinic for treatment and evaluation; follow-up data on these patients is not available. As recommended by the Center for Disease Control¹⁵ retesting was not performed in this population if the initial skin test was negative. The persistently high rate of positive tuberculin reactions nevertheless suggests that surveillance be continued in this population.

Patients of Southeast Asian origin have an increased likelihood of positive serology for Hepatitis B. Sexual partners and children of these patients should be screened, and if negative, offered immunotherapy. Infants born of Hepatitis B surface antigen-positive mothers should receive prophylactic Hepatitis B immune globulin in the immediate neonatal period.

Intestinal parasitism continues to be the most common health problem in Southeast Asian refugees. Though we were able to obtain an initial specimen for examination, there was poor compliance in obtaining follow-up stool samples and samples from family members. More stool examinations may be required to detect those parasites which shed cyclically, such as *G. lamblia*, *taenia* sp., and *Entamoeba histolytica*. The fact that the rate of parasitic infestation did not decrease with the number of years in the United States suggests that the parasites were not just carried here from overseas, but may continue to be transmitted here in the United States. As recommended by the Center for Disease Control,¹² teaching of hygienic practices will be necessary to reduce the prevalence of parasitic infections in this population.

Hematologic abnormalities are also common to this group. Although the causes of anemia were not determined, others have shown that the majority are microcytic in nature, and that thalassemias and hemoglobin E trait¹⁶ are the most common causes of microcytic anemia. Craft *et al*¹⁴ found that hemoglobin electrophoresis and serologic tests for iron stores were able to establish the etiology of anemia in 71 per cent of cases. Glucose-6-phosphate dehydrogenase deficiency is also prevalent in Southeast Asia^{9, 16} and should be considered as a possible etiologic agent of anemia. The high rate of heritable hematologic disorders, however, should alert the provider not to initiate an empiric trial of iron therapy, in a Southeast Asian refugee found to be anemic.

The high prevalence of positive VDRL testing

for syphilis bears comment. A thorough evaluation of venereal disease in this population is difficult because of cultural mores. Though it is difficult to estimate the prevalence of rape, molestation, and sexual abuse of children during this time of social upheaval, it is felt to be significantly high.¹⁷ Non-sexually transmitted diseases may result in a positive VDRL and FTA-ABS. These include pinta, caused by *Treponema carateum*; endemic syphilis, caused by *Treponema pallidum*; and yaws, caused by *Treponema pertenue*. All of these have been reported in Southeast Asia and cannot be differentiated from venereal syphilis by serologic tests alone.

Conclusion

Continued awareness of the specific disease prevalences is essential in the care of the Rhode Island Cambodian immigrant population. Our sample population has lived in the United States for about three years, and yet their disease prevalences have not shown any significant changes from the disease prevalences amongst Cambodian refugees to the United States obtained four to seven years prior to this study. We recommend, therefore, a continued surveillance and vigilance for communicable diseases in this population.

Acknowledgements

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Psychological Screening of Cambodian Refugees in a RI Primary Care Clinic

Robert T. P. Chow, MD
Seba Krumholtz, MD
Carol Landau, PhD

Screening tests performed on a sample of clinic patients of Cambodian origin, disclosed a very high rate of depression (63 per cent) and anxiety (56 per cent), somewhat more so in women than in men.

The Hopkins Symptom Checklist-25 was administered to 27 Cambodian refugees at a community health clinic in order to screen for psychiatric disorders. Sixty-three per cent of patients had positive depression scores and 56 per cent had positive anxiety scores. Women were significantly more likely to be depressed than men and were also slightly more likely to suffer from anxiety. The results are discussed in terms of previous research on refugees as well as gender and role differences.

Approximately 800,000 refugees from Southeast Asia have immigrated to the United States since 1975.¹ The circumstances surrounding this involuntary migration, the difficult conditions in the refugee camps, and the resettlement process have been implicated as the basis for the pur-

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portedly high incidence of mental illness in this population.²

Though the diagnosis of somatoform disorders and mood disorders may be clouded by substantial cultural differences,³ reliable and rapid clinical screening is still of practical import. The recently transplanted refugee patient with somatic complaints is at risk for a variety of infectious and hematologic diseases⁴⁻⁶ that are not commonly seen by the Western practitioner. In addition to an examination for physical illnesses, psychological assessment is also necessary for a comprehensive evaluation.

It is well documented that many patients in outpatient medical settings suffer from psychiatric disorders. Estimates vary, but at least one quarter of all patients in general medical practice carry psychiatric diagnoses.⁷ In addition, Mollica and associates point out that Southeast Asians are often unfamiliar with mental health practitioners and would therefore be even more likely to seek help in a medical setting.⁸ Since anxiety and depression are the most prevalent disorders found in general medical practice, the purpose of this study was to screen new patients in an ambulatory primary care setting in an attempt to determine the prevalence of these disorders and then to identify their risk factors. Women were of particular interest in this study given their increased susceptibility to depression.⁹

Methods

This study was conducted at the Central Health Center, one of the Providence Ambulatory Health Care Foundation's non-profit community-based health clinics that serve primarily the Southeast Asian community in Providence. The large majority of patients are of Cambodian descent, and the health care staff are assisted by bicultural workers. A more detailed description of this Cambodian population is reported elsewhere.¹⁰

In 1986, all new patients seen at this Center by two of the authors (S.K. and R.C.) were given

the Hopkins Symptom Checklist-25 (HSCL-25) as part of their general health assessment. This is a twenty-five item questionnaire developed by Rickels, and translated into Cambodian by Mollica *et al.*⁸ The scale screens for both anxiety and depressive symptoms and has been validated on the basis of the Diagnostic and Statistical Manual-III criteria with a sensitivity and specificity of 0.88 and 0.73 respectively, for the refugee population.

New adult refugee immigrants and new arrivals to the state were brought to the Health Center for health screening by their sponsors or family members. Of 42 potential respondents, 27 completed questionnaires, yielding a return rate of 64 per cent. Though no patient refused to cooperate, some were unable to complete the questionnaire themselves because they were unable to read Cambodian. When translators were unavailable to assist in the completion of the survey, accompanying friends and family members helped.

For each patient, the chief complaints, past medical history, demographic information, proficiency of English, laboratory results, PPD skin test status, and physical examination results were recorded. The Hopkins Symptom Checklist scores were divided into depression, anxiety, and total scores for each patient, as defined by Mollica and associates.⁸ Data were analyzed utilizing chi-square or correlation coefficient analysis.

Results

Of those who completed the surveys, 52 per cent were female and 48 per cent were male. The mean age was 42 years with a standard deviation of 12.5 years, and 66 per cent were married. Only 12 per cent were employed, and only 4 per cent were able to converse in English. The subjects had resided in the US an average of 2.3 years with a standard deviation of 1.8 years. Sixty-three percent of the patients yielded positive depression scores and of those, 65 per cent were women. Fifty-six percent of the patients had positive anxiety scores and 73 per cent of those were women.

There were significantly more women than men with symptoms of anxiety ($\chi^2=6.24$, $df=1$, $p<0.01$). Similarly, there was a trend toward women being more likely to have symptoms of depression ($\chi^2=3.04$, $df=1$, $p<0.08$). There were no statistically significant relationships between depression or anxiety and marital status ($\chi^2=1.07$, $df=3$, $p=0.78$; $\chi^2=4.83$, $df=3$, $p=0.18$). There was no relationship between the identification of a chief complaint and symptoms of depression

or anxiety ($\chi^2=0.56$, $df=1$, $p=.46$; $\chi^2=0.09$, $df=1$, $p=0.76$). High total scores on the HSCL-25 have been said to suggest the presence of emotional distress. No relationships were found between these scores, as defined by Mollica *et al.*, and age ($r=.07$), proficiency of English ($\chi^2=2.48$, $df=2$, $p=0.29$), tobacco use ($\chi^2=0.82$, $df=1$, $p=0.37$) alcohol use ($\chi^2=0.05$, $df=1$, $p=0.83$), presence of a positive PPD skin test ($\chi^2=0.94$, $df=1$, $p=0.33$), employment ($\chi^2=2.53$, $df=2$, $p=0.28$), VDRL reactivity ($\chi^2=0.64$, $df=1$, $p=0.42$), or length of time in the United States ($r=.062$).

Discussion

Mood disorders pose an important health problem among the Cambodian refugee population. Using the Hopkins Symptom Checklist as a screening instrument, a psychiatric assessment, in an ambulatory setting, was performed on a sample of Cambodian refugees.

The high prevalence of both anxiety and depression is not surprising given the traumatic circumstances of the Cambodian migration and the resettlement process. Once in the United States, most of the refugees must then struggle with poverty, unemployment, language differences, and cultural assimilation.

The lack of a correlation between such a risk factor as employment and depression may be due to the small sample size or the fact that only 12 per cent of the Cambodians in this clinic were employed. The high prevalence of depressive symptoms in this group parallels that observed in two independent Vietnamese populations. Lin E.H.-B., Ihle, *et al.*² found an overall positive depression score of 52 per cent among Vietnamese refugees, of using a Vietnamese Depression Scale. No differences were found between men and women. However, Lin K.M., Tazuma *et al.*,¹¹ who found an overall rate of positive depression scores on a Cornell Medical Index of 53 per cent identified higher rates of depressive symptoms among women and the elderly.

The finding that depression and anxiety were related to female gender is noteworthy given the small sample size. Westermeyer *et al.*¹² investigated a Hmong population in Minnesota and found a prevalence of 60 per cent of depressive symptoms. Further analysis of this population by Westermeyer *et al.*¹³ revealed that the Hmong men actually had a trend toward higher depression scale scores soon after immigration, while the Hmong women have shown gradual depressive deterioration with time.

Westermeyer *et al*¹³ postulated that the migration was much more difficult for the men, initially, because of their loss of traditional leadership positions. However, after a period of adjustment in the US, the men were able to re-establish their social roles, while the women, in general, gradually became more aware of their limited material, linguistic, and social progress. The women in this transformed culture also carried the burden of raising their non-conforming children. Women in other populations have also consistently demonstrated higher depression scores than men.⁷ Specifically, this has been documented in a study of the general Korean population in 1978 and among Chinese-Japanese-Americans in Hawaii.¹⁴ In addition, recent data by Weissman *et al* suggest that women who are unhappily married have a 25-fold greater risk of depression.¹⁵ Although marital dissatisfaction was not measured in this study, it might provide a causal link between gender and depression.

The high prevalence of mood disorders in the refugee population suggests that psychological screening should be undertaken even for those patients seeking medical care. Psychological assessment might be particularly important for patients with complaints that are not easily explained on a physical basis. Screening can be performed effectively and at low cost with the Hopkins Symptom Checklist. The Cambodian female refugees represent a particular subset of the population who are at high risk for psychiatric disorders. Treatment programs aimed at the Southeast Asian refugees with psychiatric problems need to address the special needs of the women in this population. Further analyses are necessary to determine the etiology of this gender differentiation, its progression in time, and optimal treatment regimens.

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The Risk of Lead Poisoning Among Southeast Asian Refugee Children in Rhode Island 1984-1988

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Amy Zimmerman, MPH, RD
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Chay Vang

...In conjunction with preventive and therapeutic interventions special efforts have been made to examine the epidemiologic trends of childhood lead toxicity among these SEA children in Rhode Island.

During the past twelve years, Rhode Island has become the home for more than 12,000 Southeast Asians (SEA) (Table 1). The majority of these SEA refugees have settled in Providence, predominately in areas with dilapidated housing which contain deteriorating walls covered with leaded paint. Rhode Island's Childhood Lead Poisoning Control Program (CLPCP) suspected that SEA children were therefore at higher risk for developing lead poisoning. In conjunction with preventive and therapeutic interventions,

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special efforts have therefore been made to examine the epidemiologic trends of childhood lead toxicity among these SEA children in Rhode Island.

In 1984, a pilot study was undertaken to determine whether SEA children were at greater risk than non-SEA children for lead poisoning. The statewide positive rate for all children screened in 1984 was three per cent. The positive rate for high-risk areas (eleven census tracts which constitute four Providence neighborhoods including Elmwood, South Providence, West End and Smith Hill, Mt. Pleasant) had historically been between 9-12 per cent. Results of this initial study indicated that there was a higher positivity rate among SEA children residing in high-risk areas (15.6 per cent) when compared to non-SEA children (mostly black and hispanic) living in the same high-risk areas (13.3 per cent). Both rates were higher than previously determined high-risk neighborhood rates and were dramatically higher than the statewide positivity rate. Within the SEA group the Hmong population appeared to be at significantly greater risk than the Laotian or Cambodian populations. The positivity rate of the Hmong children (28.4 per cent) was twice as high when compared to the Laotian rate (14.1 per cent) or the Cambodian rate (14.2 per cent).

In 1987, federal funds were made available to the Rhode Island CLPCP through the New England Consortium of Childhood Lead Poisoning Programs to repeat the 1984 investigation. This report will further examine the epidemiology of childhood lead toxicity amongst Rhode Island SEA children by summarizing the results of the second analysis (1987-88), comparing them to the initial analysis (1984), and documenting any epidemiologic changes that may have occurred.

Background

Rhode Island's CLPCP has coordinated statewide

Table 1. Estimates of Southeast Asian Population in Rhode Island, 1984* and 1988

Ethnic Group	1984	1988
Cambodian	3,300	6,400
Hmong	1,800	2,100
Laotian	1,000	3,000
Total†	6,100	11,500

* Rhode Island Medical Journal, 67:313-317, 1984.

† Figures do not include Vietnamese population, estimated to be about 500.

lead screening, treatment and follow-up activities since 1977. The program has established a network of approximately 100 statewide public agencies and individual providers in order to screen children (ages nine months to six years) for lead poisoning.

In addition to the lead screening which is now a part of routine pediatric primary care rendered by these agencies, the Rhode Island CLPCP also conducts a summer door-to-door screening program in the state's highest-risk neighborhoods. Bilingual outreach workers indigenous to the canvassed neighborhoods are employed to carry out the screening. This assists the CLPCP in penetrating high-risk communities and in screening those individuals who may not have received any primary health care services (many of whom are SEA) and therefore have not been screened. Since the Rhode Island CLPCP is able to screen the majority of children (nine months to six years) in the high-risk neighborhoods, its data base more accurately reflects the status of childhood lead poisoning in hard-to-reach populations.

Methods

All screening tests (usually fingerstick samples) are sent to the State of Rhode Island Laboratory where they are logged, analyzed, and entered into the laboratory's computer data base for lead. Lead levels are determined by the atomic absorption spectrophotometry (AAS) procedure and levels at or above EP (using a hematofluorometer) greater than 35 and a blood lead greater than 25 are considered to be positive. The demographic data do not include ethnicity because of incomplete information occasionally supplied by providers on the submitted laboratory slip.

The laboratory slips are then sent to the CLPCP where program staff review, classify, and take action on each slip according to program policies and procedures.

Twelve months of SEA screening results were abstracted. Since results by SEA ethnicity could

not be generated directly by the computer, an alternative methodology, using a name classification system was employed. Data were grouped by SEA ethnicity according to surname. Individual lists of children with Hmong, Laotian, and Cambodian surnames screened between July 1, 1986 and June 30, 1987, were manually identified from monthly computer printouts. Vietnamese data were not used because the state's Vietnamese population is small (500 in total) and dispersed throughout the state. Data using other Asian surnames were also excluded since these individuals tend to live in better neighborhoods which are at less risk for lead contamination.

We define penetration rate of a particular population as the number in that population screened divided by the total population, times one-hundred. In order to determine this rate for lead screening and the incidence of lead poisoning within the SEA community, base SEA population data were needed, specifically, the number of SEA children between one and six years of age living in high-risk areas. In order to extrapolate the actual number of high-risk SEA children ages one to six years, 1980 census tract data were used. Because the census only categorizes racial information into white, black and "other" and groups ages into five year cohorts (under five, five-nine, etc.) the use of this data was limited. In order then to use these data, the following methodologies were developed and applied: Data for the "under five" population in the four high-risk Providence neighborhoods where almost all the SEAs live, were totaled according to the above racial categories, (black, white, other) and were used as an estimate of the children ages one to six. In order to estimate the number of SEA children ages one to six, it was assumed that for these census tracts, the "other" category consisted totally of Hmong, Cambodian and Laotians. Therefore the estimated "other" cohort was used as the total estimated number of high-risk SEAs ages one to six. This number was then subtracted from the total estimated cohort to provide an estimate of the total number of high-risk non-SEA children ages one to six.

Total SEA population estimates were simultaneously obtained from each specific Asian Mutual Assistance Association (MAA) (Table 1). These were compared with similar estimates obtained from the State Office of Refugee Resettlement. From the estimates received, population ratios of the specific SEA ethnic groups were calculated (ie, estimated number of Hmong divided by the estimated total number of Hmong,

Table 2. Screening Volume and Yield for Lead Poisoning Southeast Asian Children, Ages 1-6 Years

Rhode Island, October, 1983 to September, 1984						
Ethnicity	Estimated Population	No. Screened	No. Positive	% Positive	Incidence [%]	Penetration Rate [%]
Cambodian	535	106	15	14.2	2.8	19.8
Hmong	350	95	27	28.4	7.7	27.1
Laotian	215	71	10	14.1	4.7	33.0
Total, Oct., 1983-Sept, 1984	1,100	326	51	15.6	4.6	29.6
Rhode Island, July, 1987 to June, 1988						
Cambodian	605	440	46	10.5	7.6	72.7
Hmong	200	123	32	26.0	16.0	61.5
Laotian	285	245	17	6.9	6.0	86.0
Total, July, 1987-June, 1988	1,090	808	95	11.8	8.7	74.1
DEFINITIONS OF TERMS USED:						
% Positive = No. Positive/No. Screened \times 100						
Incidence = No. Positive/Estimated Population \times 100						
Penetration Rate = No. Screened/Estimated Population \times 100						

Laotians and Cambodians). Having assumed that the birth rates within these communities were equal, the population ratios (18 per cent Hmong, 26 per cent Laotian, and 56 per cent Cambodian) were then applied to the estimated total number of SEA children ages one to six years (Table 2).

In order to ensure that these estimates were reasonably accurate, they were compared with estimates obtained by other means. These alternate methods included a review of birth records by Asian surnames as well as a survey of school enrollment data. The birth record extraction method produced an estimate of 1,330 SEA children ages one-six, and the school enrollment data produced an estimate of 1,120. Thus, the census data estimate of 1,090 SEA children ages one to six appears to be in the same range.

Results

In 1987 there were about 12,000 SEAs residing in Rhode Island, of which 2,100 were Hmong, 3,000 were Laotians, and 6,400 were Cambodians (Table 1). (There were an additional 500 Vietnamese who were excluded from this study.) Of these, 1,090 (9.5 per cent) are children between the ages of one and six (Table 2). Of the 1,090 SEA children in this age group, all of whom were assumed to be at risk for lead poisoning, approximately 74 per cent were screened during 1987-88, with 11.8 per cent showing abnormal screening results.

As illustrated in Table 2 (and documented as well, in the initial study), Hmong children showed the highest rate of abnormal screening results

with a positivity rate of 26.0 per cent. This is twice the rates of the Laotian and Cambodian childhood populations, where the positivity rates are 6.9 per cent and 10.5 per cent respectively (Table 2). As expected, the incidence rates within these communities follow the same pattern as the positivity rates, except that they are lower. These rates indicate that of the total number of Hmong, Laotian and Cambodian children (ages one to six) living in high-risk areas 16.0 per cent, 6.0 per cent and 7.6 per cent respectively had abnormal lead screening results. Table 2 also illustrates ethnic-specific penetration rates. The Hmong population is the least penetrated (61.5 per cent) whereas the Laotian population is the most penetrated (86.0 per cent). Although one would interpret this to mean that screening efforts are somehow unequally distributed, it is more likely that these data are reflective of the Hmong community's resistance to screening and to western medical care practices in general. Additionally, these results seem to indicate that the penetration rate is inversely proportional to the positivity rate, ie, the greater the penetration rate, the lower the positivity rate. Again, this could reflect selective differences in cultural acceptance, attitudes and understanding of the specific health care problems.

Table 2 also illustrates results from the previous study (1984) for comparison. As documented in the initial study, the Hmong children still have the highest positivity rate. Unlike the initial study, Cambodian children now have a higher rate as compared to Laotian children. The

Table 3. Screening Volume and Yield for Lead Poisoning—Rhode Island Children, Ages 1-6 Years by High or Low Risk Residence, 1987

Residence	Estimated Population	No. Screened	No. Positive	% Positive	Incidence [%]	Penetration Rate [%]
High-Risk, SEA*	1,090	808	95	11.8	8.7	74.1
High Risk, Non-SEA	3,505	2,394	94	3.9	2.7	68.3
High-Risk, Total	4,595	3,202	189	5.9	4.1	69.7
Low-Risk	51,097	14,253	238	1.7	0.5	27.9
Total	55,692	17,455	427	2.4	0.8	31.3

See Table 2 for Definition of Terms.

* SEA = Southeast Asian

positivity rates of all three groups have fallen, although the decrease in the Hmong rate is minimal (from 28.4 per cent to 26.5 per cent). Interestingly, the incidence rates do not follow the same pattern as the positivity rates over time. In all cases the incidence rates have increased between 1984 and 1988, more than doubling for the Hmong and Cambodian populations and increasing by a third for the Laotian population.

Finally, by reviewing Table 2, it can be noted that the penetration rates have greatly increased over the past four years. Two-and-a-half times as many SEA children were screened in 1987-88 as compared to 1984. More specifically, the Hmong, Laotian, and Cambodian penetration rates have increased from 27.1 per cent, 33.0 per cent and 19.8 per cent to 61.5 per cent, 86.0 percent and 72.7 per cent respectively. Overall the penetration for the SEA high risk children has increased from 29.6 per cent to 74.1 per cent. This reflects the CLPCP's efforts to screen adequately the high-risk communities in Rhode Island.

In order to determine the risk factors of lead poisoning in Rhode Island's SEA population, it is important to compare SEA and non-SEA positivity rates from the same neighborhoods (Table 3). Non-SEAs living in high-risk census tracts have a 3.9 per cent yield of positive screenings, which is one-third of that seen amongst SEAs (11.8 per cent) in the same neighborhoods, a much greater differential than existed in 1984. In 1984, the non-SEA positive rate was 13.3 per cent and the SEA positive rate for individuals living in the same areas was 15.6 per cent. Although both positivity rates have decreased, the positivity rate among non-SEA high-risk children decreased more and now more closely approaches the 1987-88 statewide positivity rate of 2.4 per cent. It is also important to note that the penetration rate in the non-SEA high-risk population is 68 per

cent. Therefore, this differential cannot be explained by assuming that the positivity rate is lower in the non-SEA population because of lesser screening. These results support the view that SEA children are at unusually high risk for abnormal lead screening results even when compared to other children living in the same deteriorated housing.

Discussion

Researchers have hypothesized that SEA children are at greater risk for lead poisoning than other children.¹ Explanations for this include the poor housing in which the majority of SEA refugees reside, the high density of lead-contaminated soil and leaded gas fumes emitted within these high-risk neighborhoods, the use of lead-glazed pottery, and the use of folk remedies which may be laden with lead.

This study has investigated the epidemiology of childhood lead poisoning in Rhode Island's SEA child population. The results, which are consistent with previous observations, indicate that the risk of developing lead poisoning is greater for SEAs than for non-SEAs even when controlling for neighborhoods of residence. Thus, it appears that there may be some forms of exposure to lead which are unique to the SEA population. Numerous investigators have stated that folk remedies are a major source of exposure to lead. However, no cases in Rhode Island have been attributed to the use of folk remedies. Presently, when the Rhode Island CLPCP investigates a SEA case, the family is questioned about the use of medications and pottery. SEAs may be afraid to reveal the use of such medicines. An investigation of the use of folk remedies in Rhode Island's SEA population is therefore warranted. Such an investigation will require a great deal of sensitivity and creativity if accurate information is to be obtained.

Cultural beliefs and attitudes need to be considered. Our community education and outreach efforts may be more effective with high-risk non-SEAs. Considering that there was a 9.4 per cent decrease in the positivity rate of the non-SEA high-risk population over the past four years one may assume that the implemented strategies may have succeeded in increasing the public awareness of lead poisoning and its preventive measures in the non-SEA population. Such educational strategies do not appear to be as successful with the SEA population, in particular the Hmong, where the penetration rate is lowest. Unpublished Rhode Island data also indicate that the Hmong have the latest entry rate into prenatal care systems among the SEA ethnic groups.

More research is needed in order to identify the unique characteristics of the SEAs which place them at unusually high risk for lead poisoning. Innovative strategies need to be developed which will bridge cultural differences and diminish the rate at which lead poisoning affects this population.

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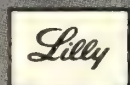
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Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a two-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy — Teratogenic Effects — Pregnancy Category C: — Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect, but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: — Studies conducted in lactating women have shown that <0.1% of the administered oral dose of nizatidine is secreted in human milk in proportion to plasma concentrations. Caution should be exercised when administering nizatidine to a nursing mother.

Pediatric Use — Safety and effectiveness in children have not been established.
Use in Elderly Patients: — Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo. Among reported adverse events in the domestic placebo-controlled trials, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A variety of less common events was also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic: — Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients and was possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L), and, in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular: — In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

CNS: — Rare cases of reversible mental confusion have been reported.

Endocrine: — Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to Axid. Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic: — Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H₂-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumentary: — Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity: — As with other H₂-receptor antagonists, rare cases of anaphylaxis following administration of nizatidine have been reported. Because cross-sensitivity in this class of compounds has been observed, H₂-receptor antagonists should not be administered to individuals with a history of previous hypersensitivity to these agents. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other: — Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine administration have been reported.

Overdosage: Overdoses of Axid have been reported rarely. The following is provided to serve as a guide should such an overdose be encountered.

Signs and Symptoms: — There is little clinical experience with overdosage of Axid in humans. Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous median lethal doses in the rat and mouse were 301 mg/kg and 232 mg/kg, respectively.

Treatment: — To obtain up-to-date information about the treatment of overdose, a good resource is your certified regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the Physicians' Desk Reference (PDR). In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance.

PV 2096 AMP

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Additional information available to the profession on request.

1. Data on file, Lilly Research Laboratories.

Advances in the Diagnosis and Treatment of Bladder Cancer

Barry S. Stein, MD

Flexible cystoscopy and DNA analysis of urinary tract cytology specimens have combined to increase both comfort for the patient and detection rates of early disease.

There have been a number of significant advances that have taken place in the diagnosis and treatment of bladder cancer over the last several years.

Diagnosis

The cornerstones of diagnosing urothelial cancer have been based on the use of intravenous pyelography, cystoscopy and urine cytology in the evaluation of patients with hematuria. Major advances have improved both cystoscopy and exfoliative urothelial cytology.

Flexible Cystoscopy: Although flexible bronchoscopes and colonoscopes have been available for many years, it is only recently that flexible instruments have been used regularly for cystoscopy.¹ In fact in our initial experience with this technique in 1984, we needed to adapt bronchoscopes for this purpose using water as an irrigation medium. The obvious advantage of flexibility is in patient comfort, because now the cystoscope will bend to conform to the urethra, rather than vice versa. Using these instruments, greater than 99 per cent of cystoscopies can be performed comfortably in the office under local anesthesia. In addition to comfort, however, we also have a better view of the entire bladder due

to both the flexibility of the instrument and its wider angle lens. An excellent view of the entire bladder including the internal urethral meatus is thus possible. Using rigid instruments, three lenses are required to obtain a similar range of visibility.

DNA Analysis of Urinary Cytology: Standard cytology of the urine has inherent limitations in detecting low grade tumors in the bladder. The reason for this is that the individual cells of a Grade I transitional cell carcinoma are so close in appearance to normal cells, that they are not perceived as abnormal. In fact Dr Gilbert Friedell, cytopathologist to the National Bladder Cancer Collaborative Group has concluded, based on extensive data, that a positive cytology, in face of a Grade I tumor means that a higher grade lesion has been missed!² In Grade II tumors, detection rates of approximately 50 per cent by cytologic means are the rule.

DNA analysis, which can be performed by two varying methods, can greatly increase these detection rates. The more popular method at this time is flow cytometric analysis.³ Cells from urinary sediment are stained with a fluorescent material, usually acridine orange, which binds with nucleic acid and hence localizes in the cell nucleus. The cells are then passed through an argon laser beam, which will cause the nuclei to fluoresce. The more DNA present, the greater the amount of fluorescence (measured as "time of flight," ie, the length of time the nucleus remains fluorescent in the laser beam). In this system 10,000 cells are measured blindly with the amount of DNA present categorized as normal complement (G0,G1), increasing DNA (S), double DNA (G2M) or aneuploidy (abnormally increased amounts) (Fig 1). In some patients, such as those with chronic cystitis, multinucleated inflammatory cells can create false positive readings. Microspectrophotometry can also measure DNA content.⁴ In this system, urinary sediment is

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Fig 1A. Normal flow cytometric pattern, with fewer than 10 per cent of cells having double DNA content (arrow).

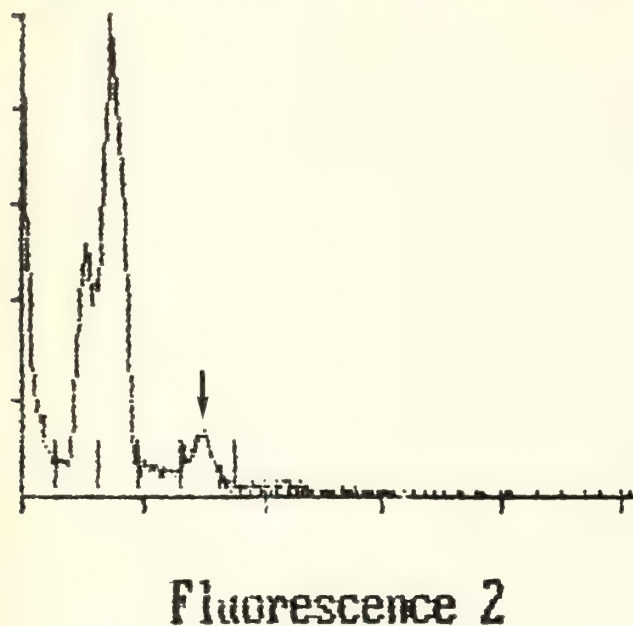
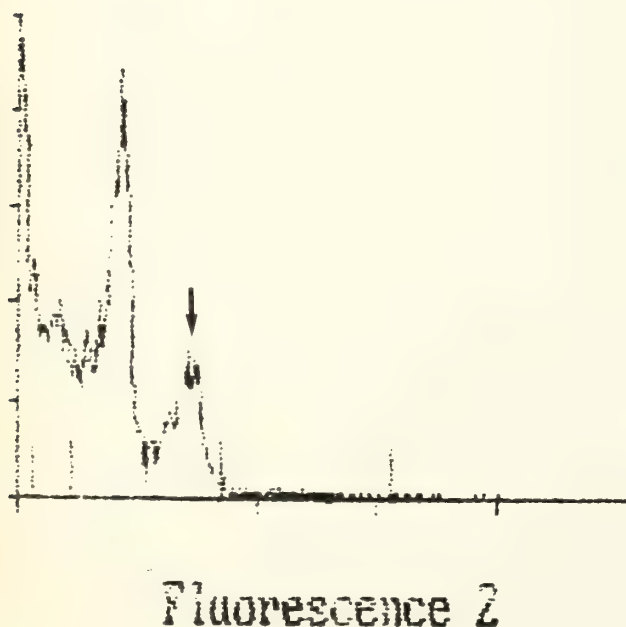


Fig 1B. Flow cytometric pattern of urinary sediment from a patient with recurrent Grade I transitional cell carcinoma. The pattern shows more than 20 per cent of cells having double DNA content (arrow).



stained with acridine orange or propidium iodide, and placed under an epifluorescent microscope (Fig 2). Fluorescence can then be measured using a photomultiplier tube on cells selected by the physician, rather than on 10,000 cells in a blinded fashion. Thus, false positive readings due to chronic inflammatory disease may be decreased. In our initial series using this technique, all Grade I and II tumors were found to be abnormal, while false positives were encountered only in patients with chronic cystitis.

The prognosis of patients with transitional cell carcinoma of the bladder has generally been determined by the standard histopathologic criteria of grade and stage. It is possible to retrieve paraffin embedded, fixed tissue, extract the nuclei and examine them for DNA analysis by one of the two procedures described above. More commonly flow cytometry has been employed. It has been shown that such measurements may prove as useful as grading or staging in determining the possibility of future recurrence or invasion. Thus, flow cytometry may become a routine adjunct to the histopathologic readings for these neoplasms.

Treatment

Superficial Transitional Cell Carcinoma: Transurethral resection of superficial tumors has been the mainstay of treatment for more than forty years. Problems with this technique include: the need for hospitalization, general anesthesia, catheter drainage, possible bleeding or perforation, and need for larger endoscopic instruments. The Nd:YAG laser represents a significant alternative to transurethral resection for bladder tumors.⁵ The laser is transmitted via a 0.4 mm quartz fiber, which can be passed through smaller instruments, even the flexible cystoscope discussed earlier (Fig 3). This allows us to reach areas of the bladder, which cannot be treated easily with the rigid resectoscope (Fig 4). Only mild warmth is perceived by the patient, so that no anesthesia is required. Since the laser does not touch the tumor, no bleeding occurs (Fig 5). We have not hesitated to perform this procedure in fully anti-coagulated patients. Since there is no bleeding, no post-operative catheter is required. Patients so treated leave the office fifteen minutes after treatment, and resume their normal activities immediately. The savings in the cost of hospitalization and anesthesia are a further benefit. There are two disadvantages, however. The first is that specialized training is required, with attendance at a laser course and hands-on

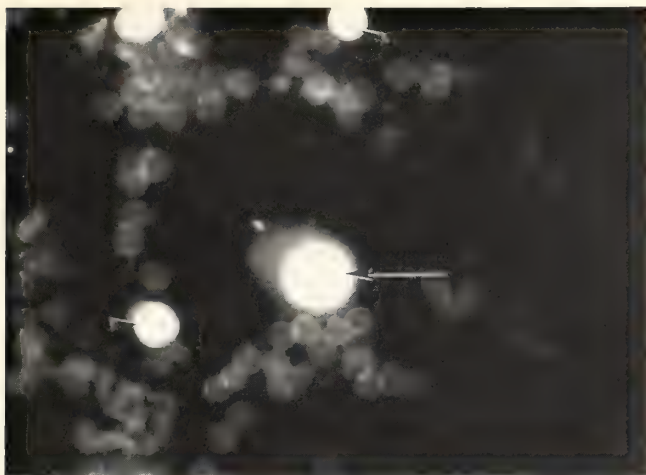


Fig 2. Urinary sediment stained with propidium iodide as seen under a microspectrophotometer. Larger nucleus (arrow) is from a malignant cell, while smaller nuclei (arrowheads) are normal in size.



Fig 3. Flexible cystoscopy with 0.4 mm quartz laser fiber (arrow) in working channel.

experience in order to master this new technology with safety. Secondly, although we biopsy after laser treatment, only the tumor grade is easily determined while staging is more difficult to assess. In patients with recurrent low-grade, low-stage lesions, however, especially when coupled with DNA analysis, this does not represent a significant problem.

Intravesical BCG: Patients with frequent recurrence of superficial bladder tumors are not at great risk of dying of their disease; however, the morbidity of treatments every three months (often resections) for recurrences can become a

Fig 4. Flexible cystoscopy with laser can reach areas inaccessible to standard resection instruments.

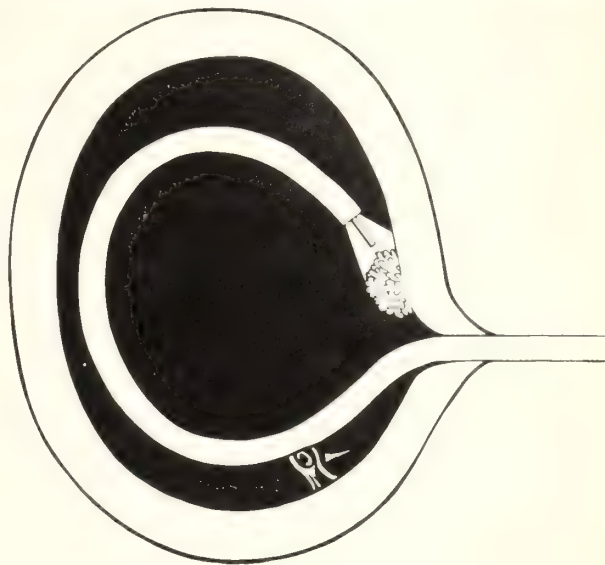
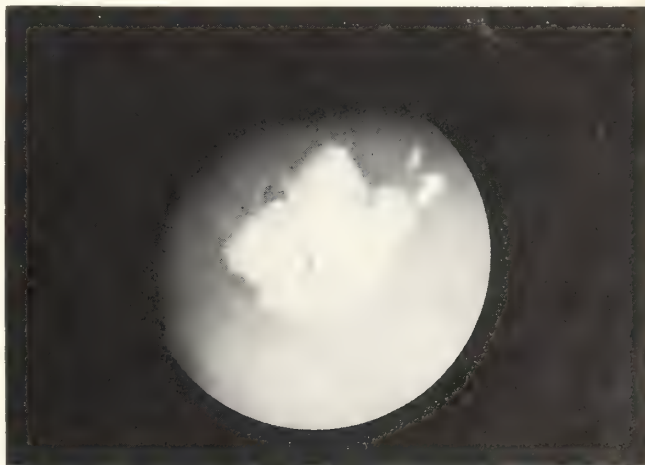


Fig 5. Appearance of bladder tumor after laser irradiation.



problem. Intravesical chemotherapy has been used for more than 20 years with Thio-tepa being the "gold standard." However, Thio-tepa produces cure rates in only approximately one-third of patients. The best second-line agent now appears to be BCG, an attenuated product of *Mycobacterium tuberculosis*. In addition, for those patients with carcinoma-in-situ of the bladder with or without superficial tumors, BCG is the intravesical therapy of choice sparing these patients from the need for radical cystectomy.⁶ Complications from earlier series included sys-

temic tuberculosis requiring triple drug therapy. With more experience, we now use lower intravesical doses and no longer use dermal scarification in addition to the intravesical instillation. Weekly instillations are administered for 6-8 weeks. The major side effect of this regimen is urinary frequency. Response rates have remained high (50-75 per cent complete response) while complications have decreased.

Invasive Disease: For patients with invasive bladder cancer, radical cysto-prostatectomy in the male and anterior exenteration in the female remain the most effective treatments. Intravesical agents, laser therapy or radiation therapy are not appropriate for surgical candidates but are reserved for patients who are poor surgical risks. Urologists, historically, have been slow to recommend this treatment because of its two major morbidities: impotence in the male and the need for a urinary stoma and bag in both sexes. Recent surgical advances have had a major impact in this area. Nerve-sparing radical prostatectomy was first described in 1983 by Walsh and Associates, and the principles were then extended to radical cystectomy.^{7,8} As many as 50-75 per cent of patients will remain fully potent after such a dissection.

The Providence Pouch, a locally designed variation of a surgically constructed neo-bladder, is described.

New concepts in neo-bladders, the so-called continent diversions, have spawned a large number of new surgical procedures.⁹ All current techniques use detubularized small or large intestine (to decrease contractions) coupled with an incontinence mechanism, and all are now named for the part of the world where they were first described. We are working on the "Providence Pouch," which uses the entire right colon and distal 15 cm of ileum to form the neo-bladder with attachment to the native urethra or vagina to produce the most natural result after cystectomy (Fig 6). Our first patient, a 42 year old man was fully potent one month post-operatively, and totally continent. We have performed three such pouches with success. These newer techniques may lead to a better acceptance of cystectomy.

Metastatic Disease: Metastatic transitional cell carcinoma was once almost universally fatal, with chemotherapy successful in less than 25 per cent



Fig 6A. Segment of right colon and distal ileum used for continent diversion.

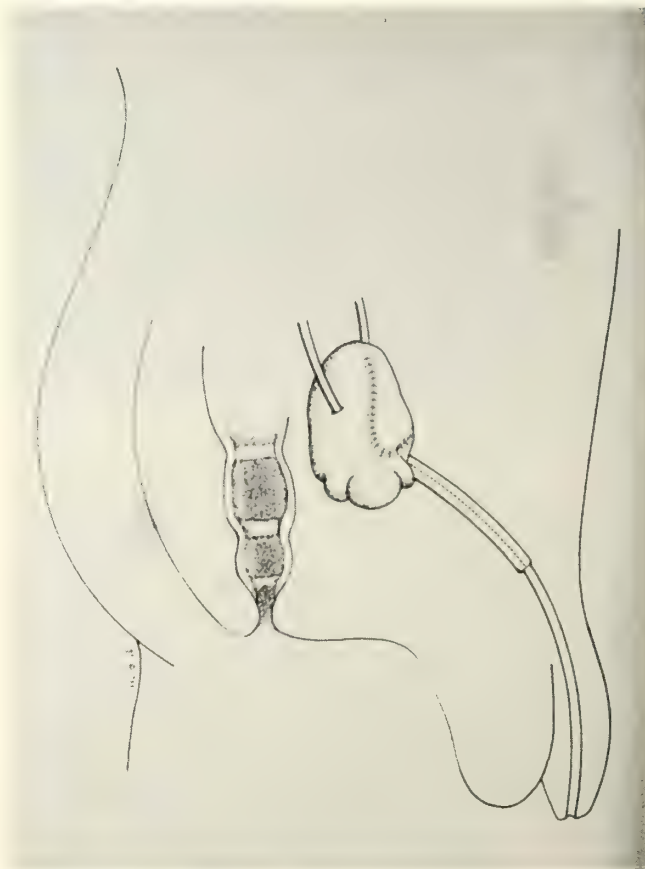


Fig 6B. Providence Pouch created and brought to native male urethra.

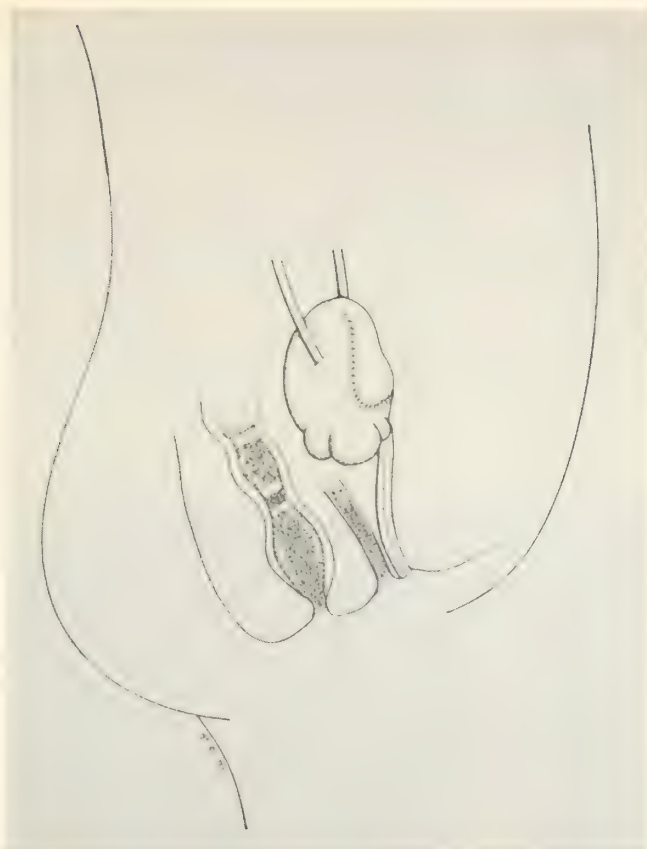


Fig 6C. Providence Pouch brought to vaginal vault in area of urethrectomy in the female.

of patients and with 4-6 month responses common. Memorial Sloan-Kettering Hospital in New York first reported on the use of a combination chemotherapy using methotrexate-vinblastine-adriamycin and cisplatin (termed M-VAC).¹⁰ For the first time, complete responses of 50 per cent and partial responses of an additional 21 per cent were being reported, both with longer response times. Other centers have now documented these results, and current studies are in progress in an attempt to obtain the ideal combination for greatest response with the least side effects. These treatments are also now being tested in a neo-adjuvant or "up front" setting, giving the drugs for two to four courses prior to radical cystectomy for high-stage tumors. Whether cure rates are increased remains to be seen, but an exciting new frontier has been opened.

Summary

There have been major advances in the diagnosis and treatment of bladder cancer in the last several years. Flexible cystoscopy and DNA analysis

have combined to increase both comfort for the patient and detection rates of early disease. The laser has become an established alternative to transurethral resection of superficial tumors, providing identical cure rates, but with more comfort and less expense. Intravesical installation of BCG has become not only an alternative treatment for recurrent superficial bladder cancer, but the first line of treatment for diffuse carcinoma in situ of the bladder which previously had been best treated with radical cystectomy. There are now numerous alternatives to the ileal conduit, when radical cystectomy is the preferred treatment. Herein we describe the "Providence Pouch," our own variation on the theme. Lastly, metastatic disease, once universally fatal, is now responding to a new combination of chemotherapy agents based on a combination of cisplatin and methotrexate.

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Highlights from the Rhode Island Medical Society's
177th Annual Dinner Dance
Blithewold Gardens, Bristol, RI
May 19, 1989



(L to R) Boyd P. King, MD (RIMS Immediate Past President), Mrs Joanne King, Mrs Terri Coustan, Donald R. Coustan, MD (RIMS President), William S. Hotchkiss (Past President, AMA).



(L to R) Boyd P. King, MD (Immediate Past President), Congressman Ronald Machtley.



Donald R. Coustan, MD
President, Rhode Island Medical Society



Richard A. Carleton, MD, Winner of RIMS' 1988 Caleb Fiske Prize for his series on the Pawtucket Heart Health Program.

COMMITTEE REPORTS

The following reports of committee activities during 1988-1989 were submitted for the consideration of the House of Delegates at its May 19, 1989 annual meeting:

Impaired Physician Committee

During the calendar year 1988, the Impaired Physicians Committee opened 15 new cases. Eight of these cases have since been closed. In total, the Committee is following 25 cases as of April 25, 1989. Nineteen individuals are currently participating in the Committee's random urine screening program. The current caseload includes one dentist and one podiatrist among the 25 individuals.

The Committee functions in conjunction with the Rhode Island Dental Association and the Rhode Island Osteopathic Society, which are represented on the Committee. Since its inception in 1978, the Committee has confronted a total of 125 physicians and dentists, as well as three medical students and one podiatrist.

The Committee, composed of 21 members, meets on the first Tuesday morning of each month.

Herbert Rakatansky, MD

• • •

Joint Medical/Legal Committee

After literally years of investigation, research and analysis, this little-known group of physicians and lawyers produced the newly-printed Interprofessional Code of Cooperation, which was distributed to all such professionals recently. The Code was officially presented at a dinner meeting at the Turks Head Club, honoring former medical society president, Dr Melvin Hoffman.

To implement the Code, the Committee is now assembling a six-person mediation committee.

Also in progress is a plan to present an annual conference in the Fall of each year.

There was an extensive discussion as to the legal effects of AIDS focusing upon legislation relating health care facilities.

Ira L. Schreiber

• • •

Mediation Committee

During the calendar year 1988, the Mediation Committee received 39 complaints against physicians, of these, 35 were closed in 1988; three were closed this year. One remains open.

As of April 6, the Committee had received six cases in the calendar year 1989; three of these have been closed, and three remain open.

Banice M. Webber, MD

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Occupational Medicine Committee

The members feel strongly that the major purpose of the committee is to discuss and comment on new bills that may affect Occupational Medicine and the Environment. Their deliberations can be used to formulate a position representing the Medical Society. A working liaison with Society administrative personnel needs to be developed to accomplish this goal.

Several members have been concerned with the effect of coal and trash-burning plants in Rhode Island on air quality, and, as individuals, have publicly commented on their concerns.

Michael A. Passero, MD

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Peer Review Committee on Physicians Competence

During the calendar year 1988, the Competency Committee received eight cases; two of these remain open as of April 25, 1989. The Committee performed three on-site visits, which included office evaluations, as part of its response to these referrals.

Three referrals have been received during the calendar year 1989. All of these remain open. The Committee will be seeking to broaden general awareness in its mission, particularly among resident physicians and other groups who can be expected to provide good referrals.

William M. Colaiace, MD

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Perinatal Committee

Our sole function over the past six-seven years has been to run an annual seminar entitled "Current Concepts in Fetal & Neonatal Care." This has been a very successful educational program and we have had an annual turnout of between 175-200 people at this meeting. This is held annually during the last week of May and I have taken the liberty of enclosing the brochure for our upcoming meeting this year.

Lorand R. Brown, MD

• • •

Publications Committee

The major concern of the Publications Committee has been the publication of the *Rhode Island Medical Journal*. Major changes that have occurred during the past year have been the resignation of Dr Goldowsky as Editor and his appointment as Editor Emeritus. Dr Stanley Aronson within the last month has been approved unanimously by the Publications Committee and ratified by the appropriate governing

bodies of the Medical Society to be the new Editor in Chief of the *Rhode Island Medical Journal*.

The committee has discussed a mission statement in an attempt to delineate clearly the role, goals, and future of the *Journal* in the coming years. This statement appeared in the June issue of the *Journal*. In addition to that, extensive changes are in the process of being made in the editorial board in an attempt to broaden and enlarge upon its expertise and involvement. Attempts are continually being made to expand the advertising base of the *Journal*.

Edward Feller, MD

• • •

The following actions were taken by the House of Delegates at its Annual Meeting held on May 19, 1989:

(a) Elected officers and committee members for 1989/1990 as recommended by the Nominating Committee.

(b) Approved a bylaw change recommendation of the Council which would abolish the Liaison Committee.

(c) Approved passage of a resolution presented by Dr. Charles Shoemaker, Jr. which reads "RESOLVED, that the American Medical Association adopt the ethical principle that prior to providing services in the elective setting, physicians should discuss with their patients the physician's role and billing policy."

(d) Approved passage of a resolution presenting the Charles L. Hill Award for 1989 to Seebert J. Goldowsky, MD.

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The Official Organ of the Rhode Island Medical Society
Issued Monthly under the direction of the Publication Committee

VOLUME I
NUMBER 1

PROVIDENCE, R. I., JANUARY, 1917

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THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

FIFTY YEARS AGO (August, 1939)

The lead article by R.O. Bowman, MD is entitled "Blood Chemical Changes in Nephritis." The author suggests the following for treatment: "1. Fluids should be forced. If edema is present sodium salts should be avoided. Sodium and chloride should be given only to replace deficiencies due to vomiting and diarrhea. Isotonic dextrose will supply fluid for excretion. 2. Transfusions or intravenous acacia solution will decrease edema and withdraw fluid from the tissues. 3. Where dyspnea results from the acidosis, sodium bicarbonate or lactate will help relieve it. 4. Feeding iron improves the anemia. 5. Adequate protein should be fed to prevent further destruction of serum proteins, and to prevent acid production by burning of body protein. The increased urea formation is not a contraindication."

The August, 1939, editorial notes the following: "During the past two years convulsive treatment with Metrazol has been used in psychiatric disorders with sufficient success to warrant continuation of the practice. At Butler Hospital in Providence 17 patients underwent this treatment between November 18, 1938 and February 6, 1939. Eight of these patients subsequently complained of pain in the back, and on roentgenological examination were found to have sustained compression fractures of the bodies of one or more of the dorsal vertebrae." The editorial continues, "It has often happened that discoveries have been made by independent observers, sometimes in far separate countries, so nearly synchronously that it has been impossible to decide who made the discovery. But priority in making this valuable discovery should be retained by the staff of Butler Hospital. They made

the first observation on December 15, 1938. They reported it before society meetings on February 13 and 16, 1939. Their paper was submitted for publication before any other."

The August, 1939, issue of the *Journal* also carries the minutes of the 128th Annual Session of the Medical Society. The Secretary, G.W. Wells, MD states: "I regret to report that eighteen of our members have died and three others have resigned. Seventeen new members have been added, making a total of 486." The Committee on Education, chaired by J. P. Eddy, 3rd., MD, in describing the efforts of the Society to provide Sunday afternoon lectures for the general public notes, "These formal lectures at the Medical Library drew only a moderate attendance. They have been falling off slightly for the past year or two possibly due to the increased interest which is taken in the radio." The report further notes, "In addition to the formal lectures your Committee this year returned the Rhode Island Medical Society to the air. Through the courtesy of Station WPRO we were given fifteen minutes every Sunday afternoon. . . . These radio lectures have apparently commanded a large audience as we have received over five hundred requests for copies of these talks from as many remote places as California, Louisiana, Maine, and Florida. . . ."

TWENTY-FIVE YEARS AGO (August, 1964)

S. Freedman, MD, and G. Settipane, MD, in the lead article entitled, "The Scratch and the Intradermal Tests in Childhood Allergy," a study

of 65 children with asthma, hayfever or both, and with clinical evidence of ragweed sensitization. The authors summarize their findings: "The purpose was to determine whether the scratch method of skin testing is sufficient and adequate in a routine evaluation of a group of children all of whom had ragweed hayfever or asthma, or both; and also how important and how often the intradermal test is necessary. Of the 65 children tested by the scratch technique, 60 gave positive immediate reactions to ragweed pollen, making intradermal testing unnecessary. Of the five patients whose scratch tests were negative, three gave small positive reactions when tested intradermally and two did not react even to intradermal testing."

An article by M. Kerzner, MD, and W. Redmon, MD, on neurotrichinosis notes the grave prognosis of the disseminated form of this parasitic disorder (a 40 per cent mortality rate). They observe, "The remarkable correlation between neurological and myocardial involvement is a distinct aid in the diagnosis of this disease which wears many masques. Early initiation of steroid therapy may prove beneficial in the treatment of neurotrichinosis."

The August, 1964, issue of the *Journal* carries a report of the actions of the House of Delegates of the American Medical Association, June 21-25, 1964, as reported by A. E. Hardy, MD, and E. T. Hackman, MD, delegates of the Rhode Island Medical Society. The Report covers Elections and Awards, Tobacco and Health ("The House approved a strong stand on tobacco and health by calling cigarette smoking 'a serious health hazard.'"), Human Rights ("The House declared itself 'unalterably opposed to the denial of membership, privileges and responsibilities in county medical societies and state medical associations to any duly licensed physician because of race, color, religion, ethnic affiliation, or national origin.'"), Physician-Hospital Relations ("... the report stresses the imperative need for the medical profession to assume responsibility for the quality, continuity, and availability of professional services and for the coordination of these services with the other essential supportive aspects of health care."), Continuing Medical Education, Cost of Medical Care ("The Commission is aware that its efforts will not result in a magic reduction in the price of medical and hospital services. It does believe, however, that its study has produced a considerable amount of new and relevant information which will serve as a basis for better understanding by the public and the

medical profession of this complex subject."), and Miscellaneous Actions ("Okayed a national conference on areawide planning of hospitals and related health facilities, to be sponsored under the auspices of the AMA").

This issue of the *Journal* publishes the text of legislation passed during the January, 1964, Session of the Rhode Island General Assembly, pertaining to the "mandatory reporting of injuries inflicted by other than accidental means upon children under the age of eighteen years," its purpose "... to protect children whose health and welfare may be adversely affected through the infliction, by other than accidental means, of physical injury requiring the attention of a physician. . . ."

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VASOTEC®

(ENALAPRIL MALEATE MSD)

VASOTEC is available in 2.5-mg, 5-mg, 10-mg, and 20-mg tablet strengths

Contraindications: VASOTEC® (Enalapril Maleate, MSD) is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor

Warnings: **Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Heart failure patients given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. Caution should be observed when initiating therapy (See DOSAGE AND ADMINISTRATION). Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in heart failure patients), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: **General:** **Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: Elevated serum potassium (> 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See Drug Interactions.)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Hypotension: **Patients on Diuretic Therapy:** Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methylglucoside, nitrates, calcium-channel blockers, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium: A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. Although a causal relationship has not been established, it is recommended that caution be exercised when lithium is used concomitantly with VASOTEC and serum lithium levels should be monitored frequently.

Pregnancy: **Category C:** There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (3.3 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters.

There are no adequate and well-controlled studies of enalapril in pregnant women. However, data are available that show enalapril crosses the human placenta. Because the risk of fetal toxicity with the use of ACE inhibitors has not been clearly defined, VASOTEC® (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome. Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension, or the underlying prematurity.

Nursing Mothers: Milk in lactating rats contains radioactivity following administration of 14 C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

HYPERTENSION: The most frequent clinical adverse experiences in controlled trials were: headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

HEART FAILURE: The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

Cardiovascular: Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, Hypotension); cardiac arrest, pulmonary embolism and infarction, rhythm disturbances, atrial fibrillation, palpitation.

Digestive: Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis.

Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Respiratory: Bronchospasm, rhinorrhea, asthma, upper respiratory infection.

Skin: Herpes zoster, pruritus, alopecia, flushing, photosensitivity.

Other: Vasculitis, muscle cramps, hyperhidrosis, impotence, blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include fever, myalgia, and arthralgia, an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Clinical Laboratory Test Findings

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis (see PRECAUTIONS). In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol %, respectively) occurred frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

Dosage and Administration: **Hypertension:** In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Hypertensive Patients with Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure: VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects.) Dosage may be adjusted depending upon clinical or hemodynamic response (see WARNINGS.)

Dosage Adjustment in Heart Failure Patients with Renal Impairment or Hyponatremia: In heart failure patients with hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine > 1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, Heart Failure, WARNINGS, and PRECAUTIONS, Drug Interactions.) The dose may be increased to 2.5 mg b.i.d. then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19386.

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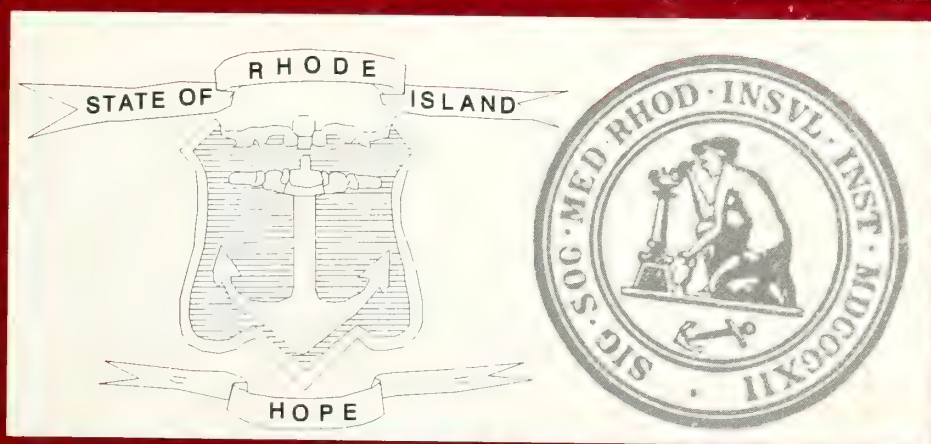
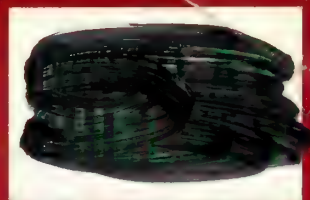
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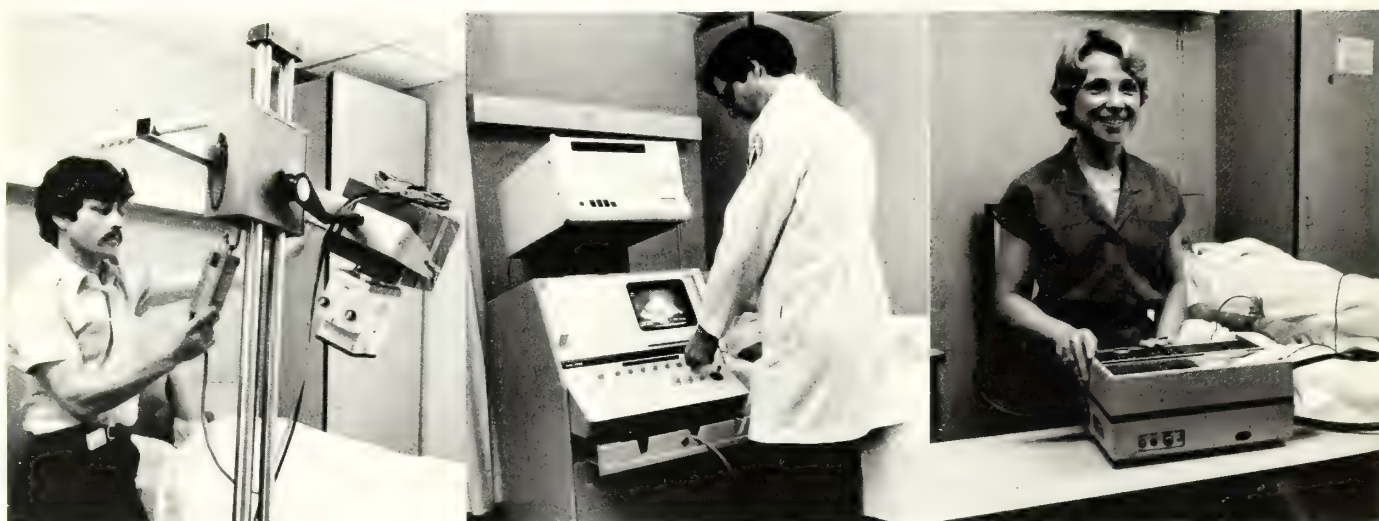


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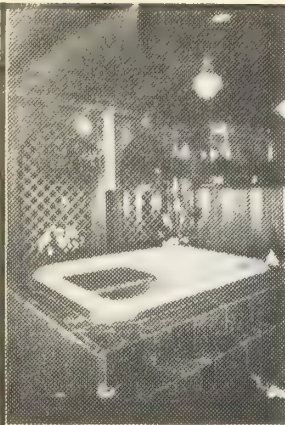
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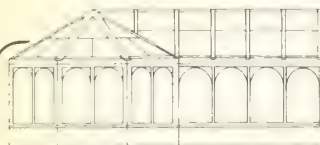
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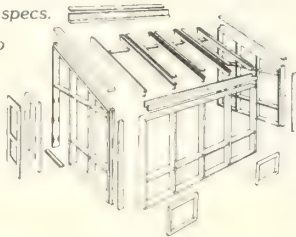
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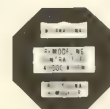


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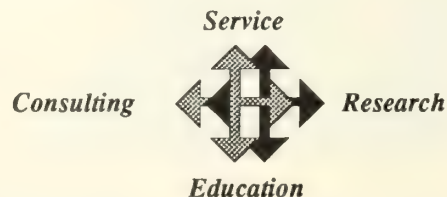
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Willie Sutton's Rule

Some years ago when the notorious Willie Sutton was brought to the penitentiary for the fourth and last time, he was asked by an enterprising newspaper reporter, "Why do you rob banks?" His reply, now immortal, was: "Because that's where the money is."

For centuries, practicing physicians have intuitively observed Sutton's basic rule as they distill their accumulating clinical experience into a personal set of operating rules. In a world where abundant diagnostic tests are available but where time and resources are quite limited, they ask, "Which test will yield the richest information?" They then select one test rather than some other because it offers them a reasonable promise of more diagnostic information: this, in their judgment, is where the diagnostic "money" is. Clinical judgment, someone observed, is the name we give to our accumulating tables of probability. Or as one Brown medical student once noted, "When you hear hoofbeats on Waterman Street don't expect to see zebras."

Clinical epidemiologists have also adopted Sutton's remorseless logic in justifying their immense labors as they gather risk-factor data. "If diseases such as cancer were to occur capriciously," they are asked, "why do you bother to invest labor and money in vast field studies? What was will not tell us what will be." In response the epidemiologists refer to their many studies which have revealed to us that most neoplastic diseases are distributed in a nonrandom fashion and that measureable factors such as gender, age, ethnicity, lifestyle, nutrition, socio-economic status,

place of residence, occupation and level of education frequently exert a significant effect upon the incidence rates and severity of these neoplasms.

The epidemiologists begin the analytic process by hypothesizing that few diseases arise "spontaneously" or by random happenstance. They then proceed to test this by observing the distribution of specific diseases in defined populations. Their studies, when meticulously pursued, have repeatedly shown that disease rates in certain subpopulations are indeed selectively increased or decreased from the overall rates when that subpopulation is associated with certain exogenous and/or endogenous factors.

The Biometry Branch of the National Cancer Institute maintains a continuing surveillance program of cancer incidence and mortality rates. The Branch periodically determines these rates in chosen US localities according to selected demographic and social characteristics. The generated data forms the basis for identifying those factors which are associated with an increase or decrease in the rate of a particular form of neoplasm. Summarized below, for example, are some annual, adjusted incidence rates of cancer per 100,000 women of the San Francisco-Oakland and Utah regions.

Crude data such as these offer the alert observer many intriguing hints concerning the etiologic mechanics of cancer. The higher rate of digestive tract cancer in the Japanese, for example, is probably related to diet since the rates

CANCER INCIDENCE RATES FOR WOMEN

Region Ethnicity	San-Francisco/Oakland				Utah White
	White	Black	Chinese	Japanese	
Digestive	58.2	63.5	57.3	70.0	41.6
Respiratory	30.4	28.1	30.1	9.2	9.3
Breast	93.2	71.8	62.7	60.9	70.0
Ut. cervix	12.0	22.2	13.9	5.2	8.0
Uterus	40.8	13.2	20.7	16.4	23.6
All sites	325.0	269.8	260.5	209.1	233.7

selectively diminish in those Japanese who adopt a totally American diet.

The overall cancer rates in San Francisco/Oakland are the highest in the nation (although there are vast differences when the rates are determined by ethnicity). The lowest rates for the white population are found in residents of Utah. Do these notable differences reflect some environmental force, regional differences in occupation or perhaps some genetic factor? Stratified studies of the Utah population yield more focussed insights. Members of the Church of the Latter Day Saints (Mormons), for example, have singularly low cancer rates, particularly lung cancer. Utah residents who are not observant members of the Church of Latter Day Saints, on the other hand, present rates which are indistinguishable from the general US public. It seems plausible therefore that some of the tenets of this church, ie, nonsmoking and avoidance of alcohol, may influence certain cancer rates. This speculation is strengthened when other nonsmoking, non-drinking communities such as Seventh Day Adventist church-members are surveyed for cancer and the same reductions in cancer incidence rates are recorded.

This issue of the *Journal* contains an important article by Fulton, Buechner and Waters who describe notable differences in the incidence and mortality rates of certain cancers between black and white women in Rhode Island. These differences prompt the authors to recommend that certain public health measures be undertaken to lessen these disparities in cancer mortality rates. As a variant of Sutton's Rule, they suggest that one added dollar invested in cancer screening and education amongst black women will generate a greater measure of cancer mortality reduction than a similar dollar invested in cancer education amongst white women. And until that day when we are provided with unlimited funds for preventive medicine in the public sector, we will be forced to rely upon the insights which epidemiological surveys provide to guide us in determining where our interventions will be most efficiently invested.

Stanley M. Aronson, MD

Collaborating in Health

This month's issue of the *Rhode Island Medical Journal* marks the introduction of a feature sub-

mitted by the Rhode Island Department of Health that will be appearing on a regular basis in the *Journal*. The Department's programs in recent years have produced a unique body of information concerning the health status, health care utilization, and health behavior of Rhode Islanders. The goal of this feature is to better disseminate the information collected by the Department in order to inform readers of the *Journal* concerning new and emerging public health issues. On a monthly basis, therefore, the *Journal* will publish a summary of statewide vital statistics for the most recent month available and a brief epidemiologic piece, entitled *Health By Numbers*, on topics of current or continuing interest.

The *Monthly Vital Statistics Reports* will include information on births, deaths, infant deaths, and fetal deaths and will present twelve-month moving totals and rates to augment the monthly data. It will be prepared by the Department's Division of Vital Records. The one-page epidemiologic studies on varied issues of compelling public health significance will originate from a wide variety of sources within the Department. They will of necessity be quick overviews of complex subjects, but they will generally be supplemented by references to other publications or to Department of Health personnel, for those readers who require more detailed information.

The monthly contribution is only one of several ways in which the *Rhode Island Medical Journal* and the Rhode Island Department of Health are pursuing a closer collaborative relationship. The Department will participate in determining the future editorial direction of the *Journal* through membership on the Editorial Board. In addition, the Department will submit three to five articles per year describing its programs and policies. Although the Department has been a regular contributor to the *Journal* in the past, this rate of publication represents an increase relative to prior periods.

Through this improved collaborative relationship, the *Rhode Island Medical Journal* hopes to increase its emphasis on public health issues and concerns, especially those with local significance. The Department of Health will improve its ability to communicate with physicians in the state, who are not only key health policy-makers and the ultimate implementers of many public health programs, but also the source of much of the information that will appear in analyzed form. The Department will also gain a rapid means of reporting fast-breaking public health problems to the medical community. It is our hope that,

through these means, the collaboration fulfills its ultimate goal — the improved health of the people of Rhode Island.

H. Denman Scott, MD, MPH
Director of Health
Rhode Island Department of Health

Stanley M. Aronson, MD
Editor-in-Chief
Rhode Island Medical Journal

Ethics, the Law and Medicine

The first in a series of commentaries on ethics, the law and medicine appears in this issue of the *Journal*. The columns will be edited by Edward Beiser, PhD, JD, the Associate Dean of Medicine [Humanities and Social Sciences] at Brown University and a distinguished jurist, medical ethicist and scholar. These discussions are published in response to a widespread appreciation that our awesome advances in scientific lore must be accompanied by an equal measure of ethical insight. As medicine becomes increasingly capable of prolonging life, of intervening in previously untried ways, and perhaps even of altering genetic destiny, be assured that we will be awash in laws, new or old, defining society's response to these increased capabilities while testing our understanding of what we think we are undertaking.

The editors of the *Journal* expect that the personal points of view expressed in these commentaries will be interesting, provocative, occasionally outrageous, but most certainly relevant to the problems and ambiguities which surround today's practice of medicine.

Readership responses to these articles are encouraged and will be published in subsequent issues.

Stanley M. Aronson, MD



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INDICATIONS AND USAGE: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40–50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics, see **WARNINGS**.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS**, **WARNINGS**, and **OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS**); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
 2. Intravenous administration of 300 to 500 mEq/hr of 10% dextrose solution containing 10–20 units of insulin per 1,000 ml.
 3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
 4. Use of exchange resins, hemodialysis, or peritoneal dialysis.
- In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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Black/White Cancer Mortality Differentials in Rhode Island: Inferences for Prevention and Screening Efforts

John P. Fulton, PhD
Jay S. Buechner, PhD
William J. Waters, Jr, PhD

... These studies identify the need for special cancer control efforts among blacks and possibly other minority and economically disadvantaged groups.

Cancer statistics in the US have been computed separately for whites and non-whites.¹⁻⁶ This practice allows for the comparison of cancer rates between groups with different average levels of education and income, as well as peoples with different genetic susceptibilities, and thus provides insights about cancer risks and access to screening and treatment.⁷ It has also permitted a more informative comparison of cancer rates among state and county populations composed of varying proportions of whites and non-whites.

Black cancer rates have been higher than white cancer rates in the US for as long as ethnically separate records have been maintained.^{1, 6} This

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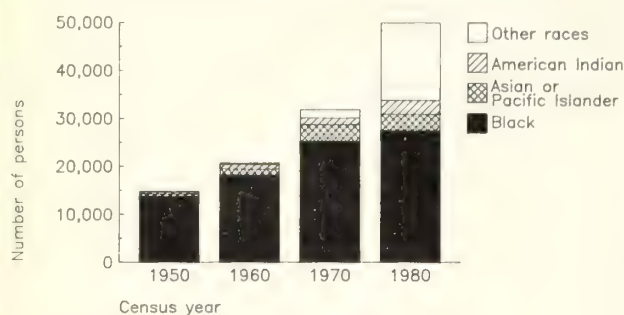
Jay S. Buechner, PhD, is Chief of the Office of Health Statistics at the Rhode Island Department of Health and a Clinical Assistant Professor of Community Health at Brown University, Providence, Rhode Island.

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is not true of all other non-white groups, however. Recent statistics from the National Cancer Institute's (NCI's) Surveillance, Epidemiology and End Results program show that rates for all cancers combined among people of Japanese, Chinese, Filipino, and American Indian ancestry are lower than cancer rates for whites.⁸ Cancer rates for native Hawaiians are higher than cancer rates for whites but lower than cancer rates for blacks.⁸ It follows that comparisons using non-white cancer rates are meaningful only insofar as the racial composition of the underlying non-white population is known. Cancer rates for non-white populations in which blacks predominate will tend to be high, while cancer rates for non-white populations in which Asians or American Indians predominate will tend to be low. Similarly, trends in non-white cancer rates will be affected by changes in the racial composition of the non-white population over time.

Rhode Island has had relatively few black, Asian, or American Indian residents over the period 1950 to 1980.⁹ As Figure 1 demonstrates, blacks have clearly predominated among non-white residents over this period, although the proportions of Asians and American Indians have grown. Between 1950 and 1960 the racial composition of the non-white population of Rhode Island remained relatively stable (Fig 1). Blacks represented 93 per cent of non-whites in 1950, 88 per cent in 1960. Between 1960 and 1970, however, the proportion of blacks decreased from 88 per cent to 79 per cent of non-whites, as the proportion of Asians increased. After 1970 this

Figure 1 — Distribution of Rhode Island's non-white population by race and census year



Source: United States Bureau of the Census; 1980 Census of Population.

trend is difficult to assess, because statistics on race from the 1970 and 1980 censuses are not comparable.⁹ In 1980 the US census changed the way it categorized the races of people of Spanish origin. As a result, many people of Spanish origin who had previously been categorized "white," and perhaps some who had previously been categorized "black" were categorized "other non-white" in 1980. The extensive use of "other non-white," a category of little meaning, compromised the already tenuous meaning of the category "non-white."⁹

Current non-white cancer statistics for Rhode Island are uninterpretable, since they depend heavily on 1980 census data. Even if this were not a problem, however, the changing composition of Rhode Island's non-white population since 1950, in addition to its recent heterogeneity, would make any interpretation of current non-white cancer statistics questionable.

Black cancer statistics offer a useful alternative to non-white cancer statistics in Rhode Island, where blacks represent the largest (and one of the oldest) racial groups among non-whites. Black statistics are far easier to interpret than non-white statistics, because they are better defined and refer to a less heterogeneous group of people. As well, 1980 census data for blacks appear not to have been affected greatly by problems in categorizing people of Spanish origin by race.⁹ If the number of Rhode Islanders of Asian or American Indian ancestry were greater, their cancer statistics would also offer useful alternatives to non-white cancer statistics. Presently, however, the numbers of Asians and American Indians in Rhode Island are so small that their cancer statistics tend to fluctuate widely from year to year, creating yet another problem of interpretation.

To assist in the identification of people at

greater risk of dying from cancer in Rhode Island, cancer death rates have been computed for whites and blacks in Rhode Island, 1975-1985, and are compared with analogous rates for the United States as a whole, gleanings which may target cancer prevention and screening efforts more effectively in the state.

... Cancer rates for non-white populations in which blacks predominate will tend to be high, while cancer rates for non-white populations in which Asians or American Indians predominate will tend to be low.

Methods

Average annual age-standardized cancer death rates by sex and race (white and black) were computed for 1975-1985 on the basis of:

- all deaths among Rhode Island residents occurring from January 1, 1975 through December 31, 1985 which had been reported to the Division of Vital Records, Rhode Island Department of Health (including the deaths of Rhode Island residents which had occurred out of state), and had been assigned an underlying cause of death coded between 140.0 and 208.9 (malignant neoplasms), using the International Classification of Diseases, 8th and 9th Editions, and
- the population of Rhode Island in 1980 by age, sex, and race, as reported by the US census.⁹

Rates were computed according to NCI specifications for cancer death rates.⁵ For each race-sex group (eg, black females):

- age-specific rates were calculated for Rhode Island;
- each age-specific rate was multiplied by the number of people in the corresponding age group of the "United States standard million populations by age for 1970," then summed over all age groups, yielding the number of cancer events (new cases or deaths) which would have occurred among 1,000,000 residents of the United States in 1970 had they experienced the 1975-1985 Rhode Island age-specific rates. This number was divided by ten to express the rate as events per 100,000 population.

Rates were computed for all cancers combined and for cancers considered amenable to control through prevention (cancers of the lung-bronchus and colon-rectum) and screening (cancers

of the breast and cervix). Cases were grouped by anatomical site according to NCI specifications for cancer death rates,⁵ based on codes of the International Classification of Diseases, 8th and 9th Revisions.

Average annual age-standardized cancer death rates by sex and race (white and black) have been computed by the NCI for the US as a whole from 1973 through 1985, using the technique outlined above.⁶ Annual rates from 1975 through 1985 were used to compute mean rates 1975-1985 by sex and race for comparison with analogous Rhode Island rates.

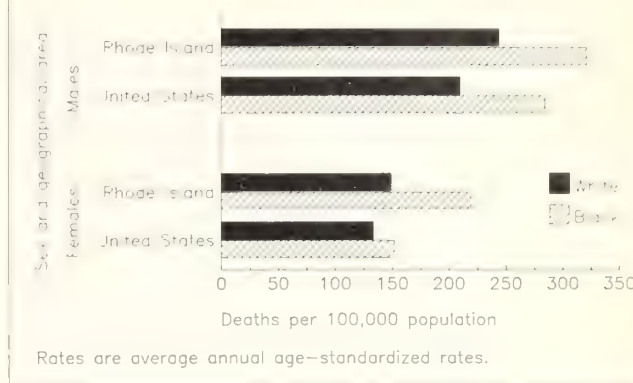
Differentials by race were expressed as percentages by subtracting white rates from black rates and dividing by white rates. Differentials by area were expressed as percentages by subtracting US rates from Rhode Island rates and dividing by US rates.

When examining rate differentials based on census data, it is important to note that census error may account for small proportions of the differentials observed. In recent US censuses, a small proportion of people were not counted, and a smaller proportion counted more than once, resulting in small net undercounts of population. Net undercount varies by age, sex, race, geographical region, and state, and has only been estimated, not measured directly. Among all the states, the Rhode Island population is estimated to have had one of the most accurate overall enumerations. (State estimates are not published with detail for age, sex, and race.) Nonetheless, estimates of nation-wide undercount in 1980 are about five percentage points higher among black males than white males in those age groups most likely to affect age-standardized cancer death rates, and from one to two percentage points higher among black females than white females in those age groups,¹⁰ causing black rates to be slightly over-estimated relative to white rates. Therefore, when rates based on 1980 US census data are found to be slightly higher for blacks than whites, the apparent differentials should be discounted as the spurious results of differential census undercount.

Results

Death rates for all cancers by sex and race in Rhode Island and the US, 1975-1985, are illustrated in Figure 2. Black rates clearly exceeded white rates during this period. In Rhode Island, the black/white differentials were substantial for both sexes: black rates were 31 per cent higher among males and 46 per cent higher among fe-

Figure 2 — Death rates for all cancers by sex and race, Rhode Island and the United States, 1975-1985



males. In the US as a whole, black rates were 36 per cent higher among males and 14 per cent higher among females. Cancer rates were substantially higher in Rhode Island than the US: 15 per cent higher among white males, 11 per cent higher among black males, 10 per cent higher among white females, and 41 per cent higher among black females.

Male death rates by cancer type and race in Rhode Island and the US, 1975-1985, are illustrated in Figure 3. Black death rates from lung cancer exceeded white rates by 40 per cent in Rhode Island and by 31 per cent in the US as a whole. In Rhode Island, lung cancer death rates exceeded analogous US rates by nine per cent among whites, and by 17 per cent among blacks. In contrast, black colo-rectal cancer death rates were about equal to white rates in both geographical areas. Colo-rectal cancer death rates were substantially higher in Rhode Island than the US: 40 per cent among white males, 46 per cent among black males.

Figure 3 — Male death rates by cancer type and race, Rhode Island and the United States, 1975-1985

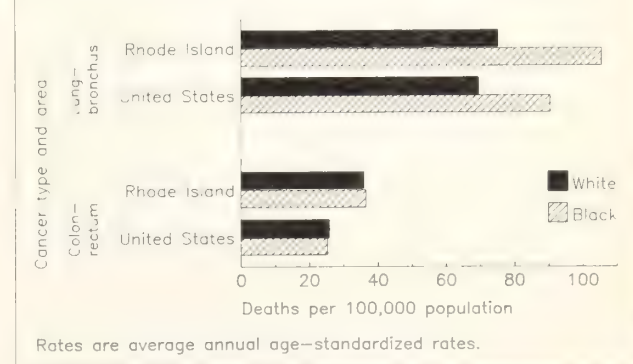
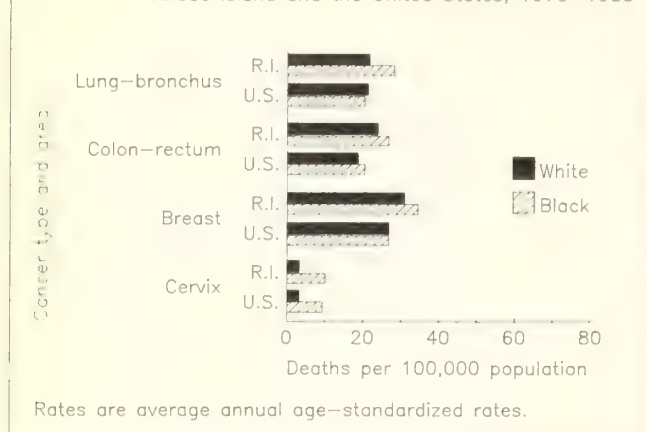


Figure 4 — Female death rates by cancer type and race, Rhode Island and the United States, 1975–1985



Female death rates by cancer type and race in Rhode Island and the US, 1975–1985, are illustrated in Figure 4. Black rates exceeded white rates from cancers of the lung-bronchus, colon-rectum, breast, and cervix in Rhode Island, and from cancers of the colon-rectum and cervix in the US. Rhode Island rates exceeded US rates, although the Rhode Island/US differential was slight for cancer of the cervix. The largest differentials by race among females were observed for cancers of the cervix (black rates were 203 per cent higher than white rates in Rhode Island and 173 per cent higher in the US as a whole) and lung (black rates were 30 per cent higher than white rates in Rhode Island).

... Rhode Island's differentials for breast and cervical cancer suggest the need for intensified cancer screening among black Rhode Island women.

Discussion

Between 1975 and 1985, inclusive, the cancer death rates of blacks substantially exceeded the cancer death rate of whites in Rhode Island. For the most part, contemporary US differentials were similar, but smaller.^{5, 6, 11} The literature on this subject suggests that racial differentials in cancer mortality are largely explained by socioeconomic differentials, except for a few cancer types.^{12, 13} The links between socioeconomic factors and health are complex, but the links between education and accurate information on prevention, screening and treatment, and the link between income and access to quality health care are central to most cancer control efforts. A recent national study revealed that blacks are less likely than whites to know about cancer and its

warning signals.¹⁴ Also, blacks are less likely than whites to have adequate health insurance.¹⁵ Although black Rhode Islanders' cancer knowledge has not been studied in depth, a recent report demonstrated that non-white Rhode Islanders are less likely than white Rhode Islanders to have health insurance.¹⁶

Rhode Island's black/white cancer differentials for breast and cervical cancer suggest that black women have benefited less than white women from recent advances in cancer screening. Black women are more likely than white women to die of breast cancer in Rhode Island. Yet reliable national data reveal that black women are less likely than white women to develop breast cancer.⁶ This disparity between low incidence and high mortality suggests that black women are less likely than white women to be screened effectively for breast cancer, or to be treated promptly and effectively once the disease is found. The national data support this suggestion, revealing that black women are more likely than white women to be diagnosed with advanced breast cancer.⁶ Black women are also more likely than white women to die of cervical cancer in Rhode Island. Despite the inference from national data that black women are more likely to develop the disease than white women,⁶ mortality from cervical cancer is considered avoidable.¹⁷ There is no reason to believe that cervical cancer screening, if performed according to current recommendations,^{18, 19} would be less effective among black women than white women. Yet national data reveal that black women are more likely than white women to be diagnosed with advanced cervical cancer.⁶ Clearly, Rhode Island's differentials for breast and cervical cancer suggest the need for intensified cancer screening among black Rhode Island women.

Recent lung cancer death rates among blacks, especially black men, have been far higher than comparable rates among whites in Rhode Island. This differential is observable in data for the US as a whole,^{5, 6} and has been attributed to higher rates of smoking among blacks.^{20, 21} Although blacks are not more likely than whites to start smoking, they are less likely to stop.²⁰ Rhode Island data on smoking differentials by race are sketchy, because recent statewide health surveys have been designed to reach a random sample of the Rhode Island population, of which only about three percent are black. Such samples include too few blacks to estimate reliable smoking rates for the black population. Nonetheless, from what is known of the epidemiology of lung can-

cer, the lung cancer experience of blacks in Rhode Island suggests an urgent need for smoking prevention and cessation programs among blacks.

Small black/white differentials were observed in colo-rectal cancer death rates among women in Rhode Island and the US as a whole. Differentials were not observed for men, who are more likely to die from this disease. More importantly, as has been noted previously, Rhode Island has higher colo-rectal cancer death rates than the US as a whole among men and women, blacks and whites, suggesting the need for dietary change among all groups in this very urban state.²²

Changes in the composition of the non-white population since 1950 have compromised the usefulness of non-white statistics for cancer surveillance in Rhode Island. Changes in US census procedures have also made "non-white" a category of ambiguous meaning. Black statistics offer a useful alternative. They are specific, they may provide insights about cancer risks and access to screening and treatment, and they are representative of the predominant racial group among non-whites in the state. In this regard, Rhode Island would be well served by demographic projections of its black population by age and sex. Also, over-sampling of black respondents in key health surveys, an uncommon practice to date, would permit greater sophistication in the evaluation of black health issues.²³

... Rhode Island has higher colo-rectal cancer death rates than the US as a whole among men and women, blacks and whites, suggesting the need for dietary change among all groups in this very urban state.

A comparison of cancer death rates between blacks and whites in Rhode Island has identified the need for special cancer control efforts among blacks and possibly other minority and economically disadvantaged groups. Three foci have been suggested: breast cancer screening, cervical cancer screening, and smoking prevention and cessation. Surveillance needs have also been suggested: projections of the black population and over-sampling of blacks in key health surveys.

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Colonic Polyps and Cancer

Hugo O. Jauregui, MD, PhD
Leila Nadra, MD
Noubar Kessimian, MD

A series of questions and answers on the terminology, classification and prognostic interpretation of colonic biopsies.

According to the latest statistic supplied by the American Cancer Society,¹ colonic carcinoma remains one of the most common malignancies in the United States, with an incidence of 160,000 cases in 1988. A close association of beef consumption and the ingestion of animal fat with the incidence of colon cancer has been documented, but there are other etiologic factors not associated with dietary habits.² For example, about 20 per cent of patients with large bowel cancer show an allele loss in chromosome 5,³ and many multiple polyposis syndromes are associated with a high incidence of colorectal cancer.⁴ In the past, the relationship between epithelial polyps and colonic carcinoma has produced a heated controversy which found its way into pertinent publications,^{5, 6, 7} and undoubtedly contributed to some confusion that still permeates the surgical management of the patient with colonic polyp(s).

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Clinical symptoms of carcinomas of the large bowel are often indicative of advanced disease and consequently the early detection of cancerous lesions is the goal of routine proctosigmoid examinations. The latter, in combination with barium enemas and guaiac stool examinations, remains the most practical method for the detection of polypoid growths.

Given a particular case of colonic cancer originating in a polyp, many of our colleagues attack the problem with timely decisions, avoiding delays in the performance of a colectomy. Nevertheless, there are others who, citing special articles advocating aggressive surgical interventions based on rather questionable figures,⁸ proceed to schedule unnecessary surgery. Some physicians on the other hand, are "sitting on" particular neoplastic entities that should be treated by appropriate surgical procedures.

One can hardly think of any other subject of tumor pathology that could be more expeditiously addressed with the consultation of a surgical pathologist, than the microscopic examination of a colonic polyp. Unfortunately, some cases, which have come to our attention for a "second look," have pathology reports that failed to properly communicate the nature of the lesion because the terminology was inadequate, outdated, or incomplete. Furthermore, other cases were well described by the pathologist, but the terms used to define the lesion carried a conceptual meaning that escaped the endoscopist. Finally, we have had gastroenterologists and surgeons who received, in a second consultation,

histological descriptions of the same colonic polypoid growth conflicting with the original report.

Regarding the colonic polyp-cancer sequence, there are two primary sources of numerous biopsies which demand from the pathologist not only a prompt and good histological diagnosis, but also a proper pathological terminology and clear definition of terms. First, there is the well known situation when a surgeon will request a positive biopsy before he/she will proceed to radical surgery for colorectal carcinoma. Second, the widespread use of the fiberoptic scope has revolutionized the approach to the treatment of the isolated polyp, which when found anywhere in the large bowel, can be removed as soon as it is detected, unless obvious contraindications exist.⁹

"I heard what you said, but I'm not sure I understand what you mean. Anyway, I don't think you're telling me what it's all about." (From dialogue around a double headed microscope during frozen section of a polyp.)

The intention of this review is to cover, through a question and answer format, the most common questions we have had in the past concerning terminology, classification, degree of malignancy, and modalities of treatment of polyps and adenocarcinoma of the large bowel.

QUESTION: Which polyps are considered neoplastic and which are not?

ANSWER: There are two types of polyps. They can have single or multiple presentation.

Firstly, we have the so-called non-neoplastic types, eg, 1) hyperplastic; 2) juvenile (retention); and 3) inflammatory (pseudopolyp) polyps. Secondly, we have neoplastic polyps that are subdivided in: a) tubular adenomas, (a more proper term than adenomatous polyps); b) villous adenomas (otherwise known as villous papillomas), and c) polyps having an equal mixture of both types of histological patterns, namely tubulovillous adenomas (or villoglandular polyps).

QUESTION: Five years ago one pathologist called a polyp we had sent him, tubular adenoma. In a second recent review, another pathologist from the same department called this polyp, tubulovillous adenoma. Apparently the slides documenting the first diagnosis were not in the file, so the block was again sectioned. Is this difference in diagnosis based on the pathologist's interpretation, tissue sampling or both?

ANSWER: Since the first slides were lost, it is possible that we will never be able to resolve this question. Proper classification of the benign histological features of a polyp is usually very easy, but on occasion it can be very difficult. Focal areas of villous configurations are not infrequent in tubular adenomas, and a well designed study showed them in 35 per cent of 76 polyps examined initially with a dissection microscope.¹⁰ The larger the tubular adenoma, the more frequent is the presence of villous changes.

QUESTION: If I understand correctly, the further conceptual extension of your last answer is that these two polyps are closely interrelated. Consequently, why is it so important to differentiate one from the other?

ANSWER: They are, in fact, interrelated. Today, most pathologists subscribe to the opinion of Morson,¹¹ who was one of the first authors to point out that most polyps start as tubular adenomas, may acquire villous features, and evolve into a pure villous growth. The fact that we have mixed forms, tubulovillous adenomas, points also to a common origin for both types of polyps. Still, the precise classification of neoplastic polyps makes sense, if we stress the fact that a very low percentage of tubular adenomas become malignant (maybe no more than 1-5 per cent), whereas villous adenomas undergo malignant transformation in 29 per cent to 70 per cent of cases. Tubulovillous adenomas have a malignancy rate of 20 per cent to 40 per cent.

QUESTION: I have followed a patient with colonic polyps for many years. So far, 25 polyps (tubular adenomas and tubulovillous adenomas) have been removed and I have found polyps in every endoscopic session that I have scheduled in the past. Is the patient going to develop cancer? Should I schedule this patient for a preventive colectomy?

ANSWER: No. A preventive colectomy is indicated for patients with familial polyposis who develop tumors earlier in life than patients with multiple tubular adenomas. A minimum of 100 polyps needs to be present for the morphological diagnosis of this condition.¹² On the other hand, the number of polyps has an important prognostic value in terms of developing cancer. Morson found that of 59 patients with multiple polyps, 12 per cent developed cancer, and the number of patients developing malignant tumors was larger when polyps were numerous.¹³ Going back to the incidence of cancer in patients with

familial polyposis, we should indicate that in these patients, the possibility of carcinoma in the rectal stump after abdominal colectomy with ileoproctostomy to preserve the anal function, makes close follow-up mandatory. In fact, the reported 59 per cent incidence of this complication in patients followed for 23 years, has moved some surgeons to recommend a proctocolectomy as the initial intervention.¹⁴

QUESTION: A 50-year-old man was examined endoscopically in my office and I removed 10 polyps, some of them measuring 1.5 cm, which were hyperplastic polyps. The patient tells me that a GI specialist in another town removed several polyps. I have requested the histopathological report which indicates that 10 previous polyps were removed in two sessions three years ago, and diagnosed as hyperplastic polyps. Is there any reason to think that hyperplastic polyps become malignant? Should I schedule this patient for more frequent endoscopic sessions?

ANSWER: Pure hyperplastic polyps do not become malignant, but carcinomas have been found containing residual adenomatous and hyperplastic epithelium.¹⁵ On the other hand, you should be aware that there is an entity called multiple hyperplastic polyposis syndrome, with relatively large hyperplastic polyps, that has been found to be associated with cancer of the colon.¹⁶ Therefore, it would be prudent to perform more frequent endoscopic examinations on a patient with multiple and/or large hyperplastic polyps.

QUESTION: I am very confused with the terminology of two previous pathological reports, and the choice of words you use for the same lesion. In the first diagnosis, a pathologist from your department called the lesion villoglandular adenoma with severe atypia. A second look by a pathologist from another hospital was reported as papillary adenoma with carcinoma *in situ*. You, on the other hand, called the same lesion a tubulovillous adenoma with severe dysplasia. What should I do? Should I "sit on" this lesion, or schedule a partial colectomy?

ANSWER: First of all, you should be aware that your problem is a common one, and a bonafide example of what we mean by confusion of terms. This lesion was well diagnosed by the two pathologists that were involved in the two previous consultations, but they used different terms. We are dealing with a polyp with a 50-50 mixture of tubular and villous patterns. Thus, following the terminology previously explained, it should be

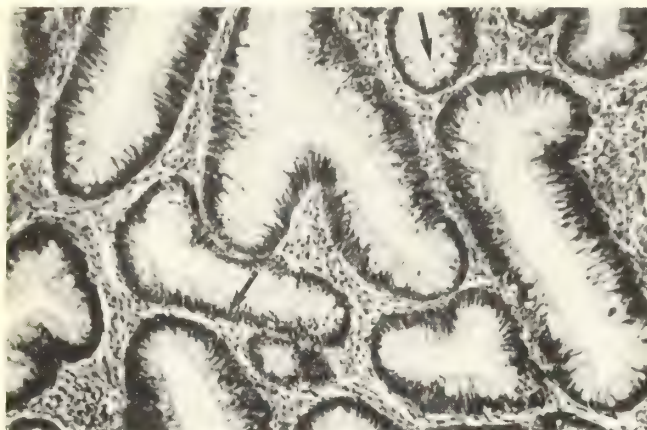
called tubulovillous adenoma. The term papillary adenoma should be avoided because it does not distinguish a tubulovillous adenoma from those having 70 per cent or more villous pattern, eg, villous adenomas or villous papillomas.

The terms dysplasia, carcinoma *in situ*, and atypia deserve a more detailed explanation. Dysplasia is a histologic and cytologic abnormality that includes cellular disorganization, cellular and nuclear pleomorphism, nuclear chromatin irregularities with increased and aberrantly located mitotic activity in epithelia.¹⁷ It is a term used most commonly by pathologists to describe lesions intermediate between normal cells and cancer in the uterine cervix. In 1983, a group of GI pathologists reviewed biopsies and resection specimens from patients with ulcerative colitis, and classified pre-cancerous changes as low grade dysplasia and high grade dysplasia, based on histological features.¹⁸ This terminology was rapidly accepted, and it is now quite common to extend it to colonic polyps as was originally proposed by Morson¹³ (See Figs 1 and 2). In this context, severe dysplasia should replace the term "carcinoma *in situ*" when severe dysplastic changes are seen *above the basement membrane* of the colonic epithelium. In fact, the use of carcinoma *in situ* on some pathological reports has moved some surgeons to follow up a polypectomy with a colon resection. This is not an academic or theoretical point since we and other fellow pathologists have seen cases of severe dysplasia in a polyp treated by a segmental colectomy, when in fact, the patient would have been cured by the excision of the polyp. Regarding the term atypia, we agree with Robert Pascal, when he states: "The introduction of the word dysplasia to describe those changes that exceeded the limits of adenomatous neoplasia, but fell short of those of invasive carcinoma, seems to be an admirable alternative to the noncommittal 'atypia' in frequent use."¹⁹ Providing that low grade dysplasia in ulcerative colitis looks like an adenomatous mucosa (see Fig 1), it follows that any tubular adenoma has a "low grade dysplasia" status.

QUESTION: A resected villous adenoma was labeled by one pathologist as carcinoma *in situ*, and by another as "intramucosal carcinoma." However, this lesion appears to be invasive. If the patient is young and barring any contraindication to surgery, it seems to me that, I should perform a partial colectomy. Is this true?

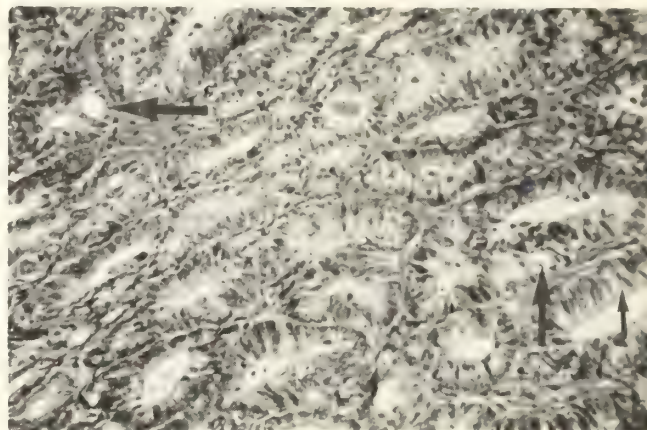
ANSWER: Again, the terminology used by these two pathologists denotes lack of uniformity in

Fig 1. Microphotograph of low grade dysplasia in tubular adenoma. Notice the hyperchromatic nuclei which are still in contact with the basement membrane (small arrow), as well as the mucin secreting cells maintaining proper polarity. (X400).



nomenclature and can be confusing in terms of the degree of penetration of the carcinomatous growth. Tumors that perforate the basement membrane, but are above the muscularis mucosa, are called carcinoma *in situ* by some prestigious surgical pathologists¹² and intramucosal carcinoma by other surgical pathologists of equal reputation.²⁰ We prefer to avoid using the term carcinoma *in situ* for colonic malignant growths because some authors use this term exclusively for malignant growths above the basement membrane (See previous question). Intramucosal carcinomas can be present in both tubular and villous polyps. When present in tubular adenomas, they may invade the stalk to a level no deeper than the muscularis mucosa (See Fig 3). It is well known that this type of invasion has never been found to be associated with lymph node metastasis.²⁰ The reason for this favorable behavior is explained by the lack of lymphatic vessels in the lamina propria of the large bowel in contrast to that of the small bowel.^{12, 20} Consequently, in the case of tubular adenomas, even with tumor invasion of the stalk, nothing other than a simple polypectomy needs to be done, provided the malignancy does not penetrate the muscularis mucosa.²¹ With a sessile villous adenoma, however, the endoscopist should be sure that the entire polyp has been resected. In this case the pathologist clearly should be warned before the gross dissection of the specimen. This is the time when a proper communication between the pathologist and endoscopist is of tremendous value. The histopathologist may report that the polyp was completely excised if he/she has found *normal surrounding mucosa in serial sections of a well oriented*

Fig 2. High degree dysplasia in a tubular adenoma. glands are overcrowded with nuclei migrating to the surface (small arrow). Mucin is secreted, on occasion, toward the basement membrane (large arrow). (X500)



specimen, as was the case in your patient. On the other hand, there are cases in which the microscopic examination of serial sections (up to 40 sections should be examined in certain polyps) cannot produce convincing evidence of the degree of penetration of the carcinomatous growth. We have had many cases of large proximally located villous adenomas, which were biopsied in small fragments that were difficult to orient in the paraffin block and even more difficult to assess in the serial H&E stained sections. Consequently, in such cases we have recommended a segmental bowel resection to rule out an invasive carcinoma (eg, a carcinomatous invasion beyond the muscularis mucosa).

QUESTION: A patient who is 35 years old has come to my office with multiple polyps (about 12 of them). The pathologist has called them juvenile polyps. Given the age of this patient, is that possible?

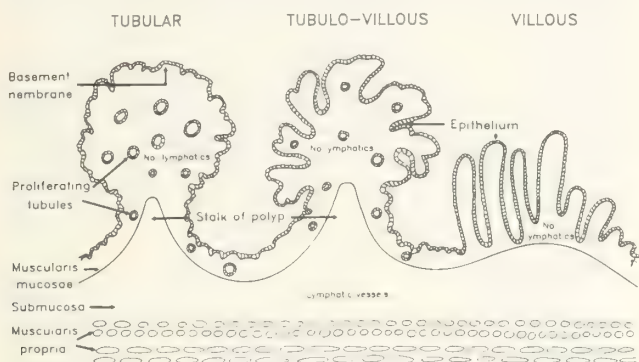
ANSWER: Yes. One third of juvenile (retention polyps) are found in adults. However, rarely do we see multiple polyps of this type throughout the bowel, such as in multiple juvenile polyposis, a condition that is associated with development of tubular adenomas and adenocarcinoma of the large bowel, duodenum, stomach, or pancreas.^{22, 23}

QUESTION: Is every colonic carcinoma preceded by a polyp?

ANSWER: This is a question that some authors will answer with a definitive yes, but we disagree with them, and we are in good company. There is histological evidence of colorectal cancers aris-

Fig 3. A) Any malignant changes above basement membrane should be referred to as mild, moderate, or severe dysplasia. The term, carcinoma in situ, should be avoided for severe dysplasia. Intraepithelial carcinoma is also used by some authors,²⁰ but we prefer to avoid the use of carcinoma in these cases.

B) Tumor cells above muscularis mucosa should be called intramucosal carcinoma.²⁰ Carcinoma in situ is used by some authors,¹² but is confusing. Probably the best way is to mention in the pathological diagnosis that the tumor has not penetrated the submucosa.



ing *de novo*. Furthermore, we agree with Rosai that there are extremely minute cancers which are not associated with polyps and lack any adenomatous changes.¹² In addition, it should be stressed that the distribution of polyps and carcinomas in the colon can differ.²⁴

QUESTION: Is there any relationship between the size of the polyps and their tendency to become malignant?

ANSWER: Yes. It is well known that polyps under 1 cm in diameter have a low incidence of carcinoma (about 1 per cent); whereas, polyps 1-2 cm in diameter have a higher cancer incidence (1-10 per cent). Furthermore, polyps greater than 2 cm have a cancer incidence of about 50 per cent.¹³

QUESTION: What is the latest information about CEA carcinoembryonic antigen (CEA) and colonic carcinoma?

ANSWER: CEA is a cancer cell glycolalix related antigen demonstrated in fetal epithelial cells, particularly the mucin secreting types.²⁵ It is present in minimal amounts in normal cells, and the use of monoclonal antibodies for its detection provides a much higher tumor specificity than polyclonal anti-CEA.²⁶ CEA disappears after tumor resection and reappears in the event of recurrence or metastasis provided the original tumor produced CEA. The highest values appear in patients with poorly differentiated neoplasms or tumor invasion of lymphatics or vessels.²⁷ Be-

Table 1. Neoplastic Colonic Polyps

Type of Polyp	Synonym	Gross and histological characteristics. Malignant Potential
Tubular adenoma	Adenomatous polyp	Usually pedunculated but may be sessile. Grossly usually under 1 cm in diameter. Low malignant potential.
Villous adenoma	Villous papilloma	Sessile, but less than 10 percent are pedunculated. Can be up to 7 cm in diameter. High malignant potential.
Tubulovillous adenoma	Villoglandular polyp papillary adenomas.	Usually pedunculated. Usually less than 4 cm. Intermediate malignant potential.

cause the CEA values can be elevated in individuals with chronic liver or renal disease, and are not elevated in the early stages of colonic neoplasia, it is not a good test for screening. In fact, some third party payers in Rhode Island will not reimburse for this procedure because they feel CEA values are nonspecific and not necessary to evaluate a patient with colon neoplasia. We find this stance unjustified since CEA testing is invaluable for monitoring therapy and early detection of metastases, and is a useful indicator for second-look surgery.²⁸ Two other tumor-associated antigens, CA 19-9 and CA 125, are used to discriminate tumor from non-tumor cells by immunoperoxidase, but anti-CEA appears to be more sensitive.²⁹

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Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.^{1,2} Also dizziness, headache, skin flushing reported when used orally.^{1,3}

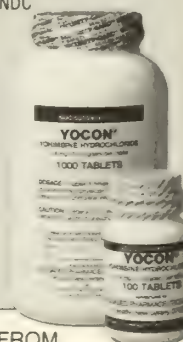
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.^{1,3,4} 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to 1/2 tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.³

How Supplied: Oral tablets of Yocon[®] 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., *New England Journal of Medicine*: 1221, November 12, 1981.
2. Goodman, Gilman — *The Pharmacological basis of Therapeutics* 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. *Weekly Urological Clinical letter*, 27:2, July 4, 1983.
4. A. Morales et al., *The Journal of Urology* 128: 45-47, 1982.

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Health Care Research on the Aged & Chronically Ill

Vincent Mor, PhD

... The major research efforts in the Center are directed toward the investigation of the diverse problems associated with the health and social service needs of the elderly and persons with chronic diseases.

Background

Reduced fertility, infant mortality and deaths due to infectious disease have drastically altered the age distribution of the US population this century.¹ Life expectancy at birth has increased nearly 30 years since 1900.² Yet all mortality gains have not been attributable only to reductions in infant mortality; life expectancy at 65 has also increased from 13.9 in 1950 to 16.9 today.² Age specific death rates for ischemic heart disease and stroke have been dropping rapidly for the past three decades even among those over 85.¹ While age-adjusted cancer mortality rates have not decreased since 1950, five year survival has increased for most cancers, meaning that patients are living with their illness for longer periods of time.³

This growing population of chronically ill and elderly in the US represents a major social policy challenge since older persons are the highest users of health-care resources; a trend that can be expected to increase over the next several decades. Advances in medical technology have positive dimensions such as increasing life expectancy and identifying diseases early enough to permit meaningful treatment, but they also raise difficult social and ethical issues about resource allocations and make it imperative that we invest wisely in health-care innovations that are cost-effective. Increasingly, medical educators have

advocated incorporating clinical epidemiology, health services research and health policy into the fabric of graduate and post-graduate education.^{4, 5} In the current public debate about changing Medicare reimbursements for physicians, Congress has recommended evaluations of the outcomes of medical care, particularly for procedures to treat the chronically ill patient.⁶

Brown University Center for Gerontology and Health Care Research

In light of these and other issues, the Brown University Program in Medicine founded the Center for Gerontology and Health Care Research. Initially funded by the Federal Administration of Aging as a consortium of academic institutions in Rhode Island and Southeastern Massachusetts with strong faculty interests in long-term care services for the aged and chronically ill, it has now evolved into the central coordinating force for multidisciplinary education and research in aging and long-term care within Brown. Currently, the major research efforts in the Center are directed toward the investigation of the diverse problems associated with the health and social needs of the elderly and persons with chronic diseases. The approach taken is based upon the premise that interventions should maximize functioning, integrate the physical and mental aspects of health, and remove barriers to service access. Research projects are undertaken in collaboration with faculty in the Brown University-affiliated hospitals and faculty from non-medical University Departments such as Sociology, Applied Mathematics and Political Science. The Center also participates in educational pro-

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grams in geriatrics and health services research at the undergraduate, graduate and post-graduate level via the Departments of Community Health, Medicine, Family Practice and Psychiatry.

Center research projects conducted over the past ten years have relied extensively on the collaboration of Rhode Island physicians and institutional health-care providers. Whether it has been referring patients to us for interview, permitting us access to hospital medical records or being randomized into control or experimental arms of a nursing home study, our experience has consistently validated the dictum that Rhode Island is a wonderful laboratory for epidemiological research.

The purpose of this article is to describe the major research themes which currently characterize the activities of Center faculty. In describing each theme, several examples of past and present research activities are presented, along with references to publications emanating from them.

Research Themes

Research studies undertaken by Center faculty revolve around the major issues in long-term care and chronic disease which range from studies of the effectiveness of interventions, to basic research on approaches, to measuring the morbidity and functional outcomes experienced by the elderly and chronically ill. Many projects have multiple components and are undertaken because of their interdisciplinary nature. This description demonstrates the range of research undertaken as well as the consistency of interests among them.

Evaluations of Innovative Interventions

This is the theme of many past and current studies undertaken by Center faculty. Much of medical practice has evolved without research on the effectiveness of new methods. Recently, greater emphasis has been placed upon studying the long term outcomes of medical care, but such large scale "field experiments" are still relatively rare. Innovations in the organization of medical care, who delivers it, how it is reimbursed and how it is regulated, can have as much of an effect on the well-being of elderly and chronically ill patients as new medical approaches.

One of the earliest evaluations conducted at the Center was the National Hospice Study in which we examined the impact of the home and hospital-based models of hospice care on the

quality of life and costs experienced by terminal cancer patients and their caregivers.⁷⁻¹⁰ The major outcomes examined were defined in terms of the function of patients and the psychosocial distress experienced by their caregivers. We relied upon interdisciplinary collaboration to expand upon existing measures of these constructs and to describe the organizational and clinical nature of the intervention.^{11, 12}

The environment in which care is provided has also been shown to have an effect on patient outcomes. Center faculty evaluated the impact of a special "Senior Care Unit" for patients 75 and over whose acute medical problems are frequently complicated by pre-existing chronic conditions as well as by cognitive and functional impairments.^{13, 14} This interdisciplinary project examined functional, cognitive and affective outcomes in the tradition of past studies of Geriatric Assessment Units.

We have also evaluated the effects of restructuring the setting in which medical oncology is traditionally provided, from inpatient to day hospital, and found that patients living at home during intensive chemotherapy suffer no untoward effects, place no greater burden on their families and prefer it to remaining in the hospital. Since cost-effectiveness is an important consideration in studying the impact of policy innovations, we compared the costs experienced by inpatient and day hospital patients and found substantial savings associated with day hospital care.¹⁵

Many aspects of medical and long-term care are regulated by state governments, particularly nursing homes. Traditionally, the emphasis has been on structural aspects of care rather than the process of patient care. To study the effect of introducing a new, patient-oriented approach to nursing home regulatory review, with the assistance of the Rhode Island Department of Health, we randomly assigned all nursing homes in the state to be reviewed using the old verses the new approach and found that the new approach yielded more patient care-related deficiencies and seemed more meaningful to both reviewers and staff.¹⁶

Other programmatic innovations we have evaluated include a health promotion program implemented for Medicare beneficiaries in Boston,¹⁷ community based case management programs for persons with AIDS in cities across the country,¹⁸ and a short term, nurse-supervised case management program for cancer patients undergoing outpatient chemotherapy.¹⁹ In each instance our approach has been interdisciplinary

and the outcomes of interest are selected domains of patient function as well as program cost-effectiveness.

Function of the Elderly and Chronically Ill Patient as an Outcome Variable

Use of function as an outcome of medical care instead of mortality or morbidity is a fairly new phenomenon, in large part pioneered by Sidney Katz, MD, former Director of the Center. The Katz Activities of Daily Living scale developed nearly 40 years ago was the forerunner of a whole class of measures of functional outcome which we at the Center continue to expand. For example, Dr Katz studied the notion of function as an outcome measure and applied actuarial methods to predict the "active life expectancy" of persons living in the community,²⁰ ie, the number of years of independent living various categories of people can anticipate. We extended the Activities of Daily Living Scale to include other instrumental functions such as preparing meals and shopping, and tasks requiring strength and stamina such as climbing stairs and carrying groceries, and found that individuals' lose the capacity to perform these tasks independently in an ordered hierarchical manner.^{21, 22}

When function is viewed as an outcome, loss of functional independence, or decline, can be seen as a morbid event with an identifiable incidence rate and risk factors. Using this perspective, Dr Katz projected the number of years persons over 65 would live before becoming impaired.²⁰ We expanded upon that initial work to include several degrees of impairment relevant to projecting need for various long-term care services. Recently, we developed projections of the degree and prevalence of functional impairment that would be present in the population 75 and over living in 2020.²³

We have addressed multidimensional aspects of human function both in the development of systems of assessing the hospitalized and frail elderly²⁴ and in refining existing scales measuring mood state²⁵ and cognitive functioning.²⁶ Recent research conducted on cancer patients at the Center has emphasized the connection between physical function and quality of life.²⁷

Currently, faculty and staff at the Center are working with a consortium of researchers in long-term care to develop and test the Congressionally mandated minimum data set for nursing home patients. This system is intended to provide a basis for assessing the quality of care by examining residents' functional outcomes. This work

is an outgrowth of earlier research examining the feasibility of using measures of functional health in nursing home populations as indicators of the quality of care provided by the homes.^{28, 29}

Developing the Science of Functional Assessment

Just as laboratory scientists must strive to perfect measurement of the processes they study, so do the clinical and social science faculty in the Center devote considerable effort to improving measures of human function. Clinical assessment of patient function requires that the assessors agree on the principles and interpret the information about patients similarly.¹⁴ The survey approach requires that questions regarding function are well calibrated and elicit precise relevant responses, since small changes in question format can make a big difference in estimates of the prevalence of dysfunction in a population.^{19, 21, 22, 24} Finally, data derived from medical records can only be as accurate as the records themselves, meaning that record quality may be the biggest determinant of observed differences in function.²⁸ Center faculty have been exploring the consistency of these different sources of data, specifically interested in whether measures of function taken from different sources yield relationships similar to other constructs such as diagnosis, length of stay and even survival.^{21, 22, 30}

Health Service Utilization Patterns

A number of Center research projects have been devoted to understanding the determinants of utilization of health services among aging and chronically ill persons. The "Cancer and Aging Study" was undertaken to examine the effect of age, function and social support on receipt of definitive cancer treatment post-diagnosis.^{31, 32} Other studies have examined the health service use consequences of falls among community dwelling elderly³³ and of functional decline.²¹ Given the concern about the high cost of medical care, many of our studies of health services use incorporate measures of total cost which can then be related to patient function, disease stage or proximity to death.^{9, 15, 17}

Another important area of service use research conducted by Center faculty is variation in health services use as a function of the course of chronic disease and aging. Specifically, studies relating changes in patient function to changes in nursing home levels of care, rehospitalization of nursing home patients and institutionalization have been completed.^{28, 29, 33}

Targetting Long-Term Care Services

In the presence of scarce resources it is crucial to assure that services are provided to those who most need them. Center faculty have studied strategies to target services to the needy. Working with the state of Connecticut, Department of Income Maintenance, Center investigators devised a "screening" instrument to identify hospitalized and community-dwelling elders applying for nursing home placement who might fare better with community services. Currently this and similar screens in other states are being tested under a grant from the Health Care Financing Administration. Several studies examining the impact of innovative delivery systems have been re-analyzed to determine whether selected subgroups of patients benefitted more or less from the interventions.^{13, 23}

A series of studies of cancer patients undergoing radiation or chemotherapy for recurrent disease has identified the prevalence of patients with "unmet" needs for assistance such as house-keeping, transportation or other tasks that, if not met, may compromise patients' ability to continue to be treated.¹⁹ The screening approach is also utilized to target interventions tested as part of a randomized trial of short term case management.

Future Research

Center faculty are currently addressing basic and applied research issues in the areas enumerated above. We are expanding our focus in several directions including greater emphasis on policy-relevant research as well as further basic research on elders' preventive health practices that might affect their risk of functional decline. We are also expanding upon our current research in Continuing Care Retirement Communities and hope to use our relationship with several such health and social service residential programs as a "laboratory" for studying patterns of functional decline and their relationship to individuals' physical, social and intellectual activities. Finally, we are very interested in forging further connections between functional and biological research on older adults.

We look forward to continuing our highly successful collaborative relationship with physicians, hospitals and nursing homes in Rhode Island. We also hope to be able to return to the health-care providing community the results of our research efforts in a form that improves the health related quality of life of the chronically ill Rhode Island population.

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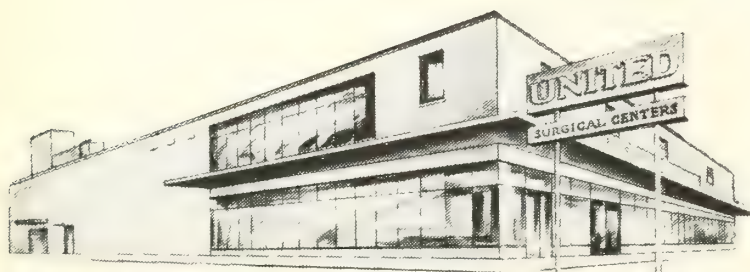
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Reports of Lyme Disease in Rhode Island have been increasing rapidly over the past several years. In fact, there has been an average annual increase of over forty-three percent. Since Lyme Disease did not become a required reportable disease until mid-1989, the increase in case reports between 1982-88 may partially reflect improved reporting as well as an increase in cases.

As with other tick borne disease, cases tend to be reported in the summer months with a peak in the month of August. Fewer new cases are reported in the colder months when the tick is not active and people tend not to have as much exposed skin.

The reporting of Lyme Disease varies geographically throughout the state. The highest rates are found in the southern section of the state and decrease towards the north and east. The town of New Shoreham (Block Island) had the highest rate in Rhode Island in 1988.

Surveillance for this disease is expected to improve with the new requirement that cases of Lyme Disease must be reported to the Rhode Island Department of Health. As well, the Health Department is sponsoring studies of tick ecology and Lyme seroepidemiology in Rhode Island.

For additional information on Lyme Disease, please refer to:

Jost EE, Rittmann MA, DeBuono BA. Lyme Disease, *Rhode Island Medical Journal* 1988;463-473.

Hyland KE, Amr ZS, Hu R. Lyme Borreliosis and Other Tick-borne Diseases in Rhode Island, *Rhode Island Medical Journal* 1988;475-486.

Figure 2
Lyme Disease Cases by Month Reported
Rhode Island, 1987-1988



Figure 1
Lyme Disease Cases by Year Reported
Rhode Island, 1982-1988

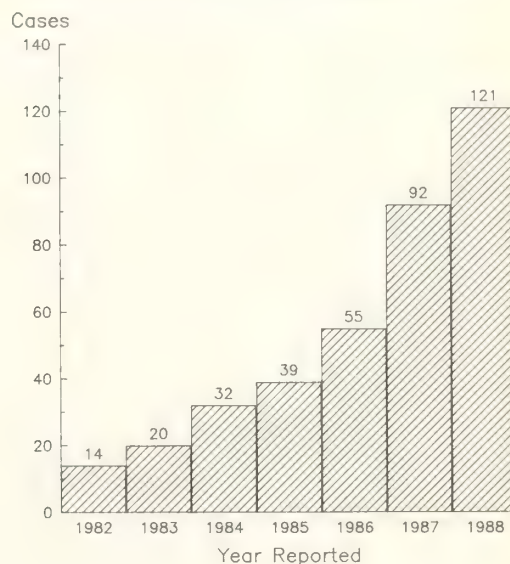
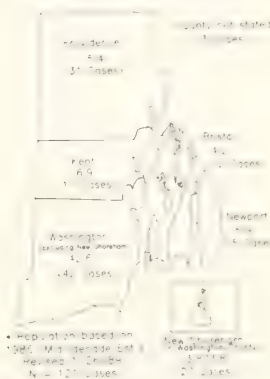


Figure 3
Lyme Disease Cases
by County of Residence
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Precautions:

- Discontinue Cecilor in the event of allergic reactions to it
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moderate to severe renal impairment are usually not required, careful clinical observation and laboratory studies should be made

- Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis
- Safety and effectiveness have not been determined in pregnancy, lactation, and infants less than one month old. Cecilor penetrates mother's milk. Exercise caution in prescribing for these patients

Adverse Reactions: (percentage of patients)

Therapy-related adverse reactions are uncommon. Those reported include

- Gastrointestinal (mostly diarrhea) 2.5%
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment
- Hypersensitivity reactions (including morbilliform eruptions, pruritus, urticaria, and serum-sickness-like reactions that have included erythema multiforme [rarely, Stevens-Johnson syndrome] and toxic epidermal necrolysis or the above skin manifestations accompanied by arthritis/arthralgia, and frequently, fever) 1.5%, usually subside within a few days after cessation of therapy. Serum-sickness-like reactions have been reported more frequently in children than in adults and have usually occurred during or following a second course of therapy with Cecilor. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome

- Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy
 - As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely
 - Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported
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State Registrar

Vital Events	Reporting Period	12 Months Ending with May 1989	
	May 1989 Number	Number	Rates
Live Births	1255	14,744	14.8*
Deaths	804	9,815	9.9*
Infant deaths	(10)	(142)	9.6†
Neonatal deaths	(8)	(104)	7.1†
Marriages	856	8,407	8.5*
Divorces	338	3,843	3.9*
Induced Terminations	594	7,716	523.3†
Spontaneous Fetal Deaths	79	1,120	76.0†
Under 20 weeks' gesta- tion	(69)	(984)	66.7†
20+ weeks' gestation	(10)	(114)	7.7†

*Rates per 1,000 estimated population.

†Rates per 1,000 live births.

Underlying Cause of Death Category	Reporting Period	12 Months Ending with February 1989	
	February 1989 Number (a)	Number (a)	Rates (b)
Diseases of the Heart	296	3,570	359.5
Malignant Neoplasms	172	2,436	245.3
Cerebrovascular Diseases	59	625	62.9
Injuries(Accident, Suicide, Homicide)	42	439	44.2
Chronic Obstructive Pulmonary Dis- ease (COPD)	26	329	33.1

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population.

NOTE: Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

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- 1) The original and one copy must be submitted by January 1, 1990 to Secretary, Caleb Fiske Fund, Rhode Island Medical Society, 106 Francis Street, Providence, Rhode Island 02903.**
- 2) All papers must be double-spaced and should not exceed 10,000 words.**
- 3) The Trustees reserve the right to award one or more prizes.**
- 4) The award recipient(s) must transfer copyright privileges to the Trustees of the Caleb Fiske Fund of the Rhode Island Medical Society. The paper will be considered for publication in the *Rhode Island Medical Journal*, subject to review by the Editorial Board.**
- 5) The award recipient(s) will be presented with the prize amount, to be determined by the Board of Trustees of the Caleb Fiske Fund, at the Annual Meeting of the Rhode Island Medical Society to be held in May, 1990.**

HARD CHOICES: Medical Ethics, Law and Health Policy

edited by Edward N. Beiser, PhD, JD

The Marcia Gray Case

What with decisions about abortion and flag-burning, the Supreme Court's just concluded term has dominated the news this spring. Hidden among the headlines was word that the Justices had agreed to review next year a Missouri case involving, as one newspaper put it, the constitutionality of the "right to die" by means of discontinuing tube-feeding.

Less than a year ago, Rhode Island found itself on the cutting edge of this major health policy issue when Chief Judge Francis J. Boyle of our Federal District Court grappled with the legal implications of the refusal of the General Hospital to discontinue the tube-feeding of Marcia Gray. In a path-breaking decision which addresses a host of ethical, legal, and policy issues, Judge Boyle ordered that the tube-feeding be discontinued. Since the Supreme Court's decision to hear the Missouri case guarantees that these issues will be widely debated, and since Judge Boyle's decision is now controlling law in Rhode Island, the Gray case is a most appropriate topic for the initiation of this column.

The editors of the *Rhode Island Medical Journal* and the author of this column claim no particular ability to stipulate those ethical norms which ought to inform the practice of medicine in our state. By instituting this column as a regular feature, they share in the widespread recognition that medicine is practiced in a social context, and that therapeutic decisions frequently involve fundamental normative choices, whether or not we choose to recognize them as such. Accordingly, the goal of this column will be to identify those ethical issues which intrude into the practice of medicine, then to subject these issues to careful analysis so as to encourage reflection and discussion. The column will have served its avowed purpose if readers find themselves struggling with these issues, and then thinking through their personal positions.

Facts of the Case

By all accounts, Marcia Gray was a lovely person. The Court proceedings described her as an active, vibrant and very happy woman who jogged regularly, read avidly, enjoyed classical music, and had a loving and supportive family. On January 4, 1986, Ms Gray, who had until that date enjoyed almost 47 years of excellent health, suffered a massive cerebral hemorrhage. Despite aggressive medical intervention including numerous surgical procedures, Ms Gray never regained consciousness and was ultimately diagnosed as being in a "persistent vegetative state." The court was advised by medical authorities that there was "no reasonable likelihood of [Ms Gray] returning to a conscious state," and further, that there was "no chance" of her recovery.

Some 16 months following the intracranial hemorrhage, her family unanimously requested her attending physician to discontinue the tube feeding [via a G-tube] and that Ms Gray be permitted to die, in conformity with unambiguous views which she had expressed prior to the onset of her current illness. The hospital refused to honor their request and litigation ensued.

The Logic of the Court's Decision:

The precise question posed by Judge Boyle was: "Whether or not the State can insist that a person in a vegetative state incapable of intelligent sensation, whose condition is irreversible, may be required to submit to medical care under circumstances in which the patient prefers not to do so." His negative response to this question was arrived at through the following sequence:

(1) Is there a federal constitutional right to refuse life-sustaining medical treatment? [Boyle concluded that there was.]

(2) Are nutrition and hydration supplied through a gastrostomy tube properly to be considered a form of medical treatment? [He concluded that they were.]

(3) Although Ms Gray is now incompetent [by virtue of her persistent vegetative state], does she retain the right to have her prior determinations respected? [The Court concluded that prior directives indeed must be honored.]

(4) Given that Ms Gray has a right to refuse medical treatment, including feeding through a G-tube, are there any competing considerations which would justify the State in overriding Ms Gray's right to refuse medical treatment? [Judge Boyle concluded that there were not, in a discussion which addresses the alleged distinctions between 'ordinary' and 'extraordinary' means of treatment, the alleged distinctions between 'withholding' and 'withdrawing' medical treatment, and the prevention of suicide.]

(5) May the General Hospital and its personnel be required to participate in a procedure which violates their own professional and ethical norms? [Judge Boyle concluded that they could.]

Legal decisions may provide the basis for ethical analysis. However, the two — law and ethics — must never be confused. Judge Boyle's opinion, which, until and unless it is reversed by a higher court, remains the law in Rhode Island, provides a convenient framework for a discussion of fundamental ethical issues. [The State of Rhode Island, probably for political reasons, did not appeal Judge Boyle's decision.]

Is Patient Autonomy Our Only Ethical Value?

For the practicing attorney, the most important aspect of the Gray case was Judge Boyle's decision that the federal Constitution includes a privacy right to refuse medical treatment, and that if a patient had made her wishes clear while she had been fully competent, that right was to be preserved despite subsequent incompetency. [The issue of prior directives — the patient's ability to decide at an earlier point what will be done later — raises an array of ethical and policy issues which this column will explore in the future.] What does this mean for the physician?

Simply, the Court asserts that the single, overriding, most important ethical norm in medical practice, is patient autonomy. In the words of the opinion, "The right to control medical decisions affecting one's body is deeply rooted in our country's history and tradition." And further, "Indeed, the right to control medical decisions affecting one's body can hardly be questioned."

Historically, of course, the Judge is wrong. American medical practice has rested on a norm of "doing good," on helping the patient. Norms

of compassion and of professional skills were thought to justify any paternalistic intervention on behalf of the patient. Judge Boyle's scholarly discussion of a constitutional privacy right certainly reflects current thinking in mainstream academic writing on medical ethics: patient autonomy — self-determination — is the overwhelming, unquestioned ethical norm. As Frank Sinatra put it [perhaps without realizing that he was describing the world of medical ethics], "I did it my way."

For Judge Boyle, and for much of the current writings on ethics, paternalism is a dirty word. While I share the belief in the importance of patient autonomy, and while my personal sympathies lie strongly with Ms Gray's family and their request, I nevertheless find the issue substantially more complex than the assertion of a privacy right alone might suggest.

George Orwell's fiction and contemporary politics provide ample reason to resist the claims of Big Brother to know what is best for us. But we ought not lose sight of the competing claim represented by the famous motto on the Christmas Seals of Father Flannagan's Boy's Town, "He ain't heavy Father; he's my brother."

Patient autonomy is, I believe, a vital and central value, deserving of respect in any discussion of ethically decent medicine. But it is not the only value. Many of the most complex of contemporary issues stem from the tension between the competing claims of autonomy and of paternalism. Surely the ethical obligation that the physician do what is in the patient's best interests, and the ethical norm that the physician conduct himself in accordance with the highest traditions and the most sophisticated achievements of his craft, are deserving of significant respect as well.

Federal constitutional rights tend to work somewhat like trump in the game of bridge. If there is a private right, then that right prevails. Medical ethics, in the real world of medical practice, tends to involve competing claims and competing considerations. Ethical dilemmas are difficult precisely because they necessarily involve legitimate values in conflict.

The limitations of the constitutional rights approach in the Gray case is particularly evident to me in Judge Boyle's very brief discussion of point (5) above. May the General Hospital and its personnel be required to participate in a procedure which violates their own professional and ethical norms? The Judge concluded that they might indeed be required to disconnect the G-tube, but on an extremely limited justification. The hospital had never warned Ms Gray's family that this

would not be an option when they admitted her; thus they were foreclosed from imposing this condition now. But the contract lawyer's argument of justified reliance will only work in this one case. In the future, hospitals would be able to notify patients in advance that discontinuation of feeding is not an option and, accordingly, they would not be bound by the Gray decision.

I suggest that the argument for patient autonomy is most compelling when the patient wants to withdraw from the care of a particular physician or institution, when the patient wants to refuse what medicine has to offer. The adult, competent member of the Church of Christ, Scientist, who for himself wishes to rely solely on the efficacy of prayer rather than prescribed antibiotics, may frustrate the concerned physician who wants to treat him with penicillin. I would protect this patient's autonomy, his right to say, "I'll do it my way," despite the compelling logic for use of an antibiotic. It is, after all, his life and I don't think the physician should impose his personal values on a resistant patient. Thus, the chart notation, "Discharged against medical advice" is a tacit recognition of the patient's autonomy.

If Marcia Gray's family had wanted to discharge her so that she might die in the privacy of her home, I think the case for the primacy of patient autonomy would have been compelling. But "I'll do it my way," is far different from "You'll do it my way."

For me, the most troubling ethical aspect of the Gray case — and I repeat that I am sympathetic to the family's wishes — was the Judge's total failure to respond to the competing claim of health professionals, and the institutions in which they labor, to be permitted to practice ethical medicine in accordance with their own norms.

The competing claim of physician autonomy is nicely put by the following case recently encountered at one of the Providence hospitals. A patient was admitted because of gastrointestinal bleeding and endoscopy seemed warranted. The patient indicated that he was an observant member of Jehovah's Witnesses, and that he would not accept a blood transfusion regardless of the medical indication. The physician responded by saying that the need for transfusion was unlikely but that there was a small possibility that the endoscopy might cause a resumption of the internal bleeding and that a transfusion might then be needed. The patient said that he understood the doctor's concerns but that he, the patient, wanted

to undergo the endoscopy but only with a guarantee, in advance, that blood products would not be administered even if the procedure resulted in a major hemorrhage.

The physician refused to undertake the procedure on these terms, and I think properly so. The seminal importance of patient autonomy leads me to respect the right of a competent adult; a member of Jehovah's Witnesses, to refuse blood products. It is his life which is at stake. If he has been fully informed of the consequences, a physician should not violate his person's right of self-determination by the involuntary administration of blood. But telling a physician that he must undertake a procedure which may cause significant bleeding while simultaneously denying him the opportunity, the right, to transfuse, is to run roughshod over the legitimate ethical claims of the physician to practice medicine in accordance with his personal value system, and his personal sense of professional responsibility.

As it happens, this conflict between the ethics of the patient and the ethics of the physician did not prove to be central to the resolution of the Gray case, since one of the surgeons who had previously treated Ms Gray was willing to disconnect the G-tube.

Thus, the claim of patient autonomy can come into sharp conflict with the claim of physician autonomy. And what of institutions? Can an institution — a hospital, a group practice, an insurance scheme, a clinic — have institutional norms and ethics? Suppose that a physician were willing to disconnect a patient's G-tube. Might the directors or the professional leadership of his hospital ever properly say to him: "That is not our understanding of how medicine should ethically be practiced."

When members of society differ sharply in their basic ethical norms, one response is to defer to individual autonomy. When some physicians in a hospital feel strongly that a given procedure is ethical (say, discontinuing G-tube feeding) and others feel that it is morally unacceptable, can the institution as such establish norms?

Future columns will explore other significant ethical questions raised by the Gray case: Is feeding properly to be considered a medical procedure? What to make of prior directives? Is there a distinction between ordinary and extraordinary care? Is there a distinction between withholding and withdrawal of medical care? And isn't this really a form of assisted suicide?



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THE RHODE ISLAND MEDICAL JOURNAL

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THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

Fifty Years Ago (September, 1939)

The Scientific Session of the 128th Annual Meeting of the Rhode Island Medical Society, convened on June 7, 1939, and is summarized in this issue. The first paper is read by Marshall Fulton, MD, Associate in Medicine at Harvard Medical School, on the Subject "Aneurism and Rupture of the Ventricle of the Heart," showing that "... these conditions occur as a result of coronary occlusion and follow coronary thrombosis in ninety per cent of the cases." The second paper, on "Ovum and Spermatozoan Age at the Time of Fertilization and the Course of Gestation and Development in Lower Animals" is read by Professor William C. Young, Biology Department, Brown University. The third paper is presented by Edgar Allen, MD, Professor of Anatomy at Yale University School of Medicine, on the subject, "Evidence from Experiments with Ovarian Hormones in Monkeys and Application to Conditions in Women." The fourth paper on the pathological aspects of spontaneous abortion is read by Arthur T. Hertig, MD, Pathologist at Boston Lying-In Hospital.

Following a buffet supper, the evening session consists of two major presentations. Elliot C. Cutler, MD, Professor of Surgery at Harvard Medical School, provides an address entitled, "Selection of Patients for Surgery." His presentation ends with the following observation. "Gentlemen, I come immediately from the bedside of a critically ill patient suffering from suppurative appendicitis, diffusing peritonitis, complete adynamic ileus, a serious postoperative pneumonia, and jaundice of possible pyelophlebitic origin. He lives today, the eleventh postoperative day, because of modern medicine and especially its chemical aspects. His fluid balance was easily achieved, but the electrolyte balance and the level

of serum proteins, dangerously threatened by ten days vomiting, are in fair shape only because of frequent blood chemical studies. The level of the sulfapyridine in his blood has been maintained by similar tests. His life thus far and his hope of life from now on are dependent on our chemical knowledge and clinical chemical tests. If such a spectacular case fixes my remarks in your memory, remember also that similar tests will prepare your patient for surgery, will give you positive information as to the risks he is to run and will prevent disasters. I beg of you to become chemically and physiologically minded."

A second evening paper, entitled, "Circulatory Collapse and Shock" was given by Soma Weiss, MD, Professor of Medicine at Harvard.

• • •

New members of the House Staff at Rhode Island Hospital include: August H. Clagett, Jr, MD, J. J. Ross, MD, Carl S. Sawyer, MD, Herman I. Riddell, MD, Howard Trafton, MD, Morris Goldenberg, MD and Scott L. Tarplee, MD.

• • •

There is no mention made of the invasion of Poland by the German armies on the first day of this month, the beginnings of World War II.

Twenty Five Years Ago (September, 1964)

The lead article is entitled, "Diazepam (Valium[®]) in Cerebral Palsy," and assesses the value of diazepam in reducing skeletal muscle hypertonia and body anxiety associated with cerebral palsy. Eric Denhoff, MD, the author, concludes that "Valium is a good skeletal muscle relaxant drug. . . . However, the differences in placebo reports by different observers point out the need

to continue a complex double blind procedure for these types of medications since both neurological and emotional elements must be considered in the final evaluation."

The second original article, "Diagnosis and Management of Caustic Esophageal Burns at the Rhode Island Hospital," written by Mary D. Lekas, MD, describes the etiologic background of such cases, the effects of varying therapeutic regimes in thirty cases and states in summary: "The majority of caustic burns of the esophagus in young children are caused by ingestion of commercial preparations of 95% sodium and potassium hydroxide. Since adopting the use of steroids and antibiotics at the Rhode Island Hospital, we have been able to eliminate bougienage."

The third article entitled, "Alcoholism: A World Problem," is authored by Laurence A. Senseman, MD who concludes: "I find from my long experience with problem drinkers that they are treatable in spite of failures and frustrations, if one expresses an interest in them as persons and learns the stresses which exist in their environment and in their interpersonal relationships. If we could know what is going on in the drinker's life, especially when he begins his drinking episodes, and what dynamics are activated by his environmental and inner stresses, we could perhaps predict such episodes and theoretically at least take measures to reverse them. In the alcoholic, every psychological and psychiatric disorder is encountered. If we could but understand this and treat psychiatrically the underlying causes in each individual patient with a broad therapeutic approach, then this could be a challenging new frontier for psychiatry in the next decade. If we treat the patient well psychiatrically, he will not have to treat himself alcoholically."

A brief case report by Raymon S. Riley, MD, Andrew Platthy, MD, and Lester L. Vargas, MD, describes a 38 year old woman with presumed mitral stenosis who was found at open heart surgery to have a left atrial myxoma.

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A small footnote item: The Department of Commerce notes that the American public spent during the past year \$15.7 billion on hospitals, physicians and drugs. During the same interval, the public spent \$24.7 billion on liquor, tobacco and cosmetics.

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Abbreviations: The *Journal* attempts to avoid the use of jargon and abbreviations. All abbreviations, especially of laboratory and diagnostic procedures, must be identified in the text.

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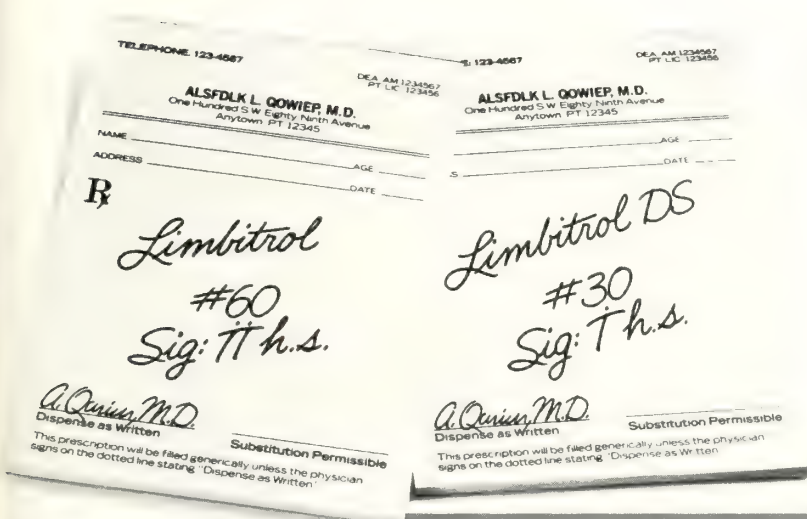


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Withdrawal symptoms of the barbiturate type have occurred after discontinuation of benzodiazepines (see Drug Abuse and Dependence).

Precautions: Use cautiously in patients with a history of seizures, in hyperthyroid patients, those on thyroid medication, patients with impaired renal or hepatic function. Because of suicidal ideation in depressed patients, do not permit easy access to large quantities of drug. Periodic liver function tests and blood counts recommended during prolonged treatment. Amitriptyline may block action of guanethidine or similar antihypertensives. When tricyclic antidepressants are used concomitantly with cimetidine (Tagamet), clinically significant effects have been reported involving delayed elimination and increasing steady-state concentrations of the tricyclic drugs. Use of Limbitrol with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Should not be taken during the nursing period or by children under 12. In elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects. Inform patients to consult physician before increasing dose or abruptly discontinuing this drug.

Adverse Reactions: Most frequent: drowsiness, dry mouth, constipation, blurred vision, dizziness, bloating. Less frequent: vivid dreams, impotence, tremor, confusion, nasal congestion. Rare: granulocytopenia, jaundice, hepatic dysfunction. Others: many symptoms associated with depression including anorexia, fatigue, weakness, restlessness, lethargy.

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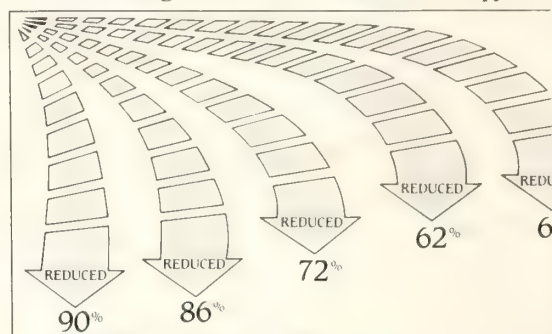
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RHODE ISLAND MEDICAL JOURNAL



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The Floppy Infant Syndrome

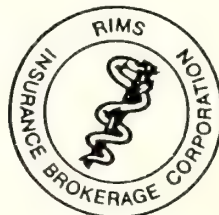
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Cover: *This month's issue of the Journal is devoted entirely to the Floppy Infant Syndrome. The photo is courtesy of Gloria D. Eng, MD, with George Washington University and Children's Hospital National Medical Center, Washington, DC. See story page 367.*

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The Floppy Infant Syndrome

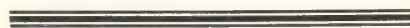
The first published reports of severe, sustained infantile hypotonia, or floppiness, appeared about 100 years ago in the German medical literature. In 1891, Werdnig reported on a hypotonic illness in two siblings. Their separate births were normal but after a few months each brother developed a progressive, symmetrical muscle hypotonia and weakness, eventually with obvious muscle atrophy and visible fibrillations; no sensory, cognitive or sphincteric impairments were described in these infants. In 1893 Hoffman described four infants with a similar pattern of deteriorating spinal muscular atrophy. Again, the hereditary character of the disorder, seemingly transmitted as an autosomal recessive trait, was evident. Some years later, in 1900, Oppenheim published a very brief account of a hypotonic syndrome of infancy (later called amyotonia congenita) which seemed to be materially different from the disorder defined by Werdnig and Hoffman in at least three clinical features. Oppenheim's infants were hypotonic at birth while the Werdnig-Hoffman infants were said to be normal at birth but then slowly developed a limpness and weakness during their first year of life; the hypotonic state was either stable or diminishing in Oppenheim's patients while it continued to worsen with the Werdnig-Hoffman group; indeed, most of the later died of respiratory infection within the first six years of life. Finally, the Oppenheim cases showed no apparent familial tendencies in contrast to the obvious hereditary nature of the disease in the Werdnig-Hoffman families.

Despite these striking differences, were these two disorders truly distinguishable clinicopathological entities? In the ensuing decades large numbers of cases were accumulated and studied longitudinally. Many were submitted to detailed autopsy examination. Most serious observers concluded that they were studying essentially the same disease representing an underlying atrophic disorder of motor neurons, principally spinal (akin in some ways to amyotrophic lateral sclerosis of adults), and that there was no rational

justification for separating infantile spinal muscular atrophy (Werdnig-Hoffman) from amyotonia congenita (Oppenheim). But these more comprehensive studies revealed further that there were yet other demonstrable causes of floppiness in the infant, some congenital and some antenatal, some neurologic, some myopathic and some even endocrinologic in origin, yet all of which were quite separable in etiology and prognosis from the Werdnig-Hoffman-Oppenheim complex. Thus, what began as an attempt to reduce infantile hypotonia to a unitary neural disorder provided us instead with an exceedingly complex set of pathophysiologic substrates only some of which can be attributed to motor neuron disability.

Sustained floppiness in an infant is a complicated matter, puzzling to the pediatrician and certainly dismaying to the parent. This issue of the *Journal*, guest edited by Edwin Zalneraitis, MD, a distinguished pediatric neurologist, with contributions from medical centers in Washington, Philadelphia and Hartford, is devoted almost totally to this perplexing clinical problem.

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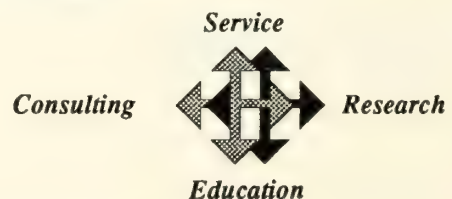
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The Pathophysiology of the Floppy Infant

Edwin L. Zalneraitis, MD

The floppy infant has been recognized as a clinically unique and challenging patient.

Introduction

Floppiness, or low muscle tone, is a sensitive indicator of illness in an infant. It is, however, a non-specific sign. Infants can present with hypotonia due to nervous system disorders, muscle disease, genetic disorder, endocrinopathies, metabolic disease or virtually any acute, intercurrent illness. For this finding to be useful, the clinician must be able to localize and diagnose the source of the loss of muscle tone.

This paper addresses the pathophysiology of hypotonia developmentally, with particular emphasis on those aspects that are clinically useful in the diagnosis and treatment of the floppy infant. Elsewhere in this issue of *The Rhode Island Medical Journal*, other authors have reviewed some of the important areas of diagnosis and management of these infants in more detail. Maguire and Sladky have concentrated on the diagnostic dilemmas of motor unit diseases. Since many processes that present with infantile hypotonia are inherited, DiMario has summarized the current genetic understanding of some important disorders resulting in hypotonia of infancy. McDonald has provided a personal and professional account of the difficulties in parenting a floppy infant, and Eng has reviewed the very important topic of the rehabilitation and care of children with persistent hypotonia.

The Developing Motor System

As the nervous system develops, the central and peripheral motor components simultaneously

mature. This is reflected in muscle,¹ the target organ of this process. Premyoblastic mesenchymal cells that accumulate in the first weeks of life become myoblasts between five and eight weeks of gestation. However, mature myocytes do not appear until 15 to 20 weeks post-conception, and these first differentiate into histochemically distinct fiber types between 20 and 24 weeks gestation, with the concomitant maturation of complete motor units. With this neurodevelopmental transformation, movement that was barely detectable by ultrasound imaging is changed to movements that are readily sensed by the pregnant woman.

The maternal perception of fetal movements normally increases in frequency and intensity from their first detection to parturition. The opportunity to observe this motor behavior directly arises when normal premature infants are reared in neonatal intensive care units from 23 weeks of gestation onward.

The acquisition of voluntary movement control, generally recognized after 44 weeks conceptual age, proceeds from head to foot, and proximal to distal. The earliest movements, starting around 20 weeks gestational age, represent the development of tone, power and reflex. These occur progressively from the lower to the upper body, and they reflect the maturation and organization of the spinal cord. During this time, motor units further mature, as seen in the changing histochemical patterns in developing muscle. Tendon stretch responses become discrete and localized. Recognition of this developmental pattern provides a standard from which the abnormalities of early motor development can be discerned.

Prior to the onset of willful movements, as term approaches, motor unit activity is further orga-

Edwin L. Zalneraitis, MD, is Assistant Professor of Pediatrics and Neurology at the University of Connecticut Medical School, Farmington, Connecticut.

nized by the development and activation of a certain brainstem and spinal cord tracts. These tracts direct a series of stereotyped, integrated and automatic behaviors that include grasping and extension of toes and fingers following ventral and dorsal stimulation, and feeding responses of rooting, snouting and sucking. Several other of these integrated activities have been localized to specific tracts from the brainstem to the spinal cord. These include the rubrospinal tract which produces the flexion posture of term infants (prior to inhibition by cerebellar input), the vestibulospinal tract which facilitates the tonic neck responses, and the reticulospinal tract which mediates improved tone with alertness by its influence on gamma motor neurons in the anterior horns of the spinal cord.² When these integrated activities fail to appear, serious failure of basic nervous system organization is to be suspected. When they persist beyond normal expectation, a disorder of voluntary movement (eg, cerebral palsy) should be considered. Once suppressed by the voluntary motor system, the reappearance of grasping, feeding and the other integrated reflexes suggests a degenerative process affecting the voluntary motor system.

The earliest movements represent the development of tone, power and reflex.

Voluntary motor activity is mediated through a complex system that controls the thalamus, and refined by the cerebellum and basal ganglia. The influence of this system is hard to recognize in the neonate, and the functioning of all the components does not begin to become evident until late infancy. The influence of the voluntary nervous system in the neonate is vaguely recognized by the loss of persistence of the integrated activities and the failure of reinforcement of the muscle tone. Later in infancy, it is recognized by the failure of acquisition of willful movements in a timely and characteristic fashion. A summary of the major phases of motor development is presented in Table 1.

Hypotonia and the Developing Nervous System

Mature individuals, like infants, lose muscle tone when they develop nervous system disease, have severe intercurrent illness or simply sleep. However, the extent, severity and duration of hypotonia is strikingly greater in an infant than in an older child or adult with a similar process. This is due directly to the immaturity of the nervous system, and it thus makes the etiology of the low

Table 1. Clinical Stages of Motor Development

Age	Localization	Manifestation
20-30 weeks PCA	motor unit	tone, power, reflex
36-44 weeks PCA	brainstem-spinal cord tracts	integrated, automatic responses
1 month- 20 years	above the motor unit	voluntary movement

PCA — post-conceptual age

muscle tone harder to localize and diagnose during infancy. For this reason, the floppy infant has been recognized as a clinically unique and challenging patient.

Dubowitz³ defined a floppy infant by three clinical features: unusual postures, diminished resistance of joint to passive movement, and increased range of movements of the joints. He divided hypotonic infants into two major groups: Those with muscle weakness who had motor unit disease, and those without muscle weakness. The latter group of infants had central nervous system disease, connective tissue disorders, genetic alterations, metabolic diseases, endocrinopathies, and chronic non-nervous system disease such as congenital heart disease. Physiologic hypotonia of the premature infant was also mentioned.

Findings other than weakness, however, can be important in recognizing hypotonic infants with motor unit disease, especially sick or premature neonates. Hypoactive or absent tendon stretch reflexes and contractures can be extremely helpful signs in recognizing this group of infants. Respiratory and feeding impairment are more typical of infants with motor unit disease, and these infants are more likely to have impaired ocular or facial movements than infants with non-motor unit disease. Muscle atrophy occurs with motor unit disease, but it is often hard to detect in infants. In addition, muscle wasting is common in sick infants whose nutritional needs are excessive. Finally, children with motor unit disease are less likely to show signs of brain or spinal cord impairment. Some disorders of the motor unit such as the mitochondriopathies do involve the central nervous system also, and children with motor unit disease have increased risk of perinatal injuries to the central nervous system such as asphyxia or spinal cord injuries due to hyperextension of the neck. Table 2 summarizes the distinguishing features between motor unit and non-motor unit disease.

As infants and their motor system mature, the level and etiology of impairment become easier to identify. Except in cases of disruption of cerebellar integration, the hypotonia of brain and spinal cord disease are replaced by spasticity. The hypotonic children with cerebral palsy are clearly distinguished by extrapyramidal movement disorders, particularly ataxia, and abnormal tendon stretch responses. Central nervous system impairment is also identified by complications such as delayed cognitive development and seizures. Dysmorphic features become more clearly distinguished from the deformations that occur secondary to motor unit impairment. Connective tissue diseases become more apparent in the commonly recognized sites such as skin, joints and the vasculature. Endocrinopathies and metabolic problems are revealed by laboratory results or the advancing consequences of untreated disease. Those infants with benign transient hypotonia or physiologic hypotonia of the premature infant improve in tone, power and voluntary control.

Evaluating the Floppy Infant

Guided by the knowledge of expected motor development and the clinical features distinguishing motor unit from non-motor unit disease, an appropriate evaluation of the floppy infant can be planned.⁴

The physical examination of the infant is the most important and the first step in this process. Passive observation of the infant reveals hypotonia by abnormal posture. The infant will often lie with limbs abducted and extended. Contractures may be obvious, but more subtle limitations should be sought by passive stretching of the limbs. Loss of power can be apparent by decreased power and frequency of spontaneous movements. For example, the weak child may not be able to overcome gravity with spontaneous

effort. Power can be assessed further with such benign stimulation as the squeezing of a nail bed. This allows the examiner to detect the power of withdrawal readily. The hypotonic child with motor unit disease will make an effort that is commensurate with the reduction in muscle tone, while the child with non-motor unit impairment typically generates a withdrawal response beyond that predicted from the hypotonia. Tendon stretch responses are best elicited in infants at the pectoralis muscles, the leg adductors, and the ankles by tapping the examiner's thumb placed just medial to the axilla, on the medial knee, or the sole of the foot respectively. Observing for facial weakness can be facilitated by gently blowing on the face. Attractive objects and the doll's eyes maneuver are used to assess for ophthalmoplegia. Paraspinal stroking (Gallant reflex) should be done in alternating short segments along the back. A sensorimotor response should be elicited, and a flare to stroke should be seen afterward. This, combined with intact anal wink and no urinary dribbling, verifies spinal cord integrity. Observation of feeding effort is an important part of the examination, and it is separate from assessment of suck. During the entire evaluation, respiratory competence should be evaluated, but an arterial blood gas or infant pulmonary function tests are often needed to supplement these observations. Central nervous system abnormalities are often revealed during the examination, most commonly in the form of altered consciousness in the neonate, delayed cognitive development in the older infant, or seizures. Comparing the results of this physical assessment to the findings for motor unit and non-motor unit disease in Table 2, should allow for

Table 2. Localization of Infantile Hypotonia

Finding	Motor Unit	Non-motor Unit
muscle strength	decreased	normal
reflexes	decreased/absent	normal/ increased
contractures	often present	rarely present
facial weakness	more likely	unlikely
ophthalmoplegia	more likely	unlikely
respiration	more likely	unlikely
impaired		
feeding impaired	more likely	less likely
muscle atrophy	common	uncommon
CNS involvement	uncommon	common

Table 3. Non-motor Unit Causes of Infantile Hypotonia

1. Central nervous system disease (congenital encephalopathies)
2. Metabolic alterations
 - A. abnormal chemical homeostasis
 - B. inborn errors of metabolism
 - C. intoxications
 - D. endocrinopathies
3. Genetic diseases (other than inborn errors)
 - A. chromosomal disorders
 - B. dysmorphic syndromes
4. Connective tissue disorders
 - A. Ehler-Danlos Syndrome
 - B. osteogenesis imperfecta
 - C. chondrodysplasia
5. Systemic illnesses
 - A. acute—sepsis, trauma, etc.
 - B. chronic—eg, congenital heart disease

proper localization of the offending process in almost all cases.

If the findings suggest a motor unit process, ie, motor neuron, nerve, neuromuscular junction or muscle disorder, it is appropriate to proceed with an examination of family members, particularly the mother. Disorders such as neonatal myotonic dystrophy or congenital fascioscapulothoracic dystrophy will be recognized best in this way. If no diagnosis is evident by examining family members, a serum creatinine phosphokinase may be obtained. This may be elevated by the trauma of delivery alone, and caution is needed in the interpretation of this test. An electromyogram and nerve conduction studies can diagnose myotonic and myasthenic disorders, and they can help localize the level of motor unit impairment for planning a biopsy of muscle or nerve as needed. This evaluation is discussed in detail in this issue of the *Journal* by Maguire and Sladky.⁵

If the initial evidence suggests non-motor unit disease, the evaluation may be considerably broader in scope. Table 3 shows a list of the categories of disease to be considered. The most common of all causes of infantile hypotonia is acute encephalopathy, particularly of hypoxic-ischemic origin. Systemic illnesses may cause low muscle tone in infants, but metabolic diseases, genetic disorders and connective tissue diseases need to be considered when the diagnosis is not clearly apparent from the initial history, examination or laboratory results.

Encephalopathy is defined by altered consciousness or seizures. History or examination often point to ischemic, traumatic or infectious causes. Laboratory evaluation should include a structural examination of the brain by cranial ultrasound, computed tomography, or magnetic resonance imaging. An electroencephalogram can help define the extent and prognosis of these disorders. A lumbar puncture is indicated when infectious disease or metabolic disorders of lactic acid or glycine are considered. Disorders such as systemic infections, renal compromise, pulmonary disorders or cardiac disease are usually evident on physical or laboratory examination. A careful examination for dysmorphic features is always part of the evaluation, and chromosome analysis should be performed in selected cases. Connective tissue disorders are usually apparent by hypermobility of joints, distensibility of skin, or secondary deformity.

Conclusions

Hypotonia is a sensitive sign of illness in infants. Floppiness in an infant results in a diagnostic dilemma that can be best solved by first considering it in the context of normal infant motor development, and then by distinguishing those infants likely to have motor unit disease from those who do not. Specific diagnostic, genetic, parenting and management issues, presented elsewhere in this issue of the *Journal*, need to be addressed as part of the care of these infants.

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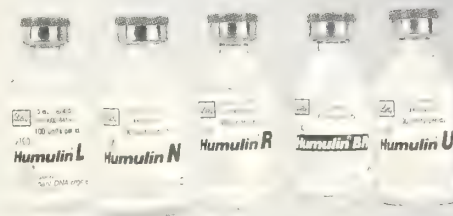
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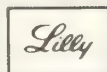
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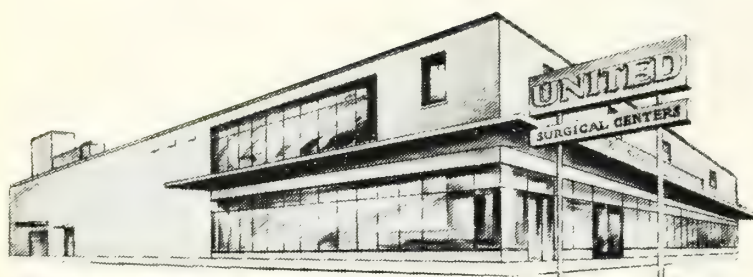
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Genetic Diseases in the Etiology of the Floppy Infant

Francis J. DiMario, Jr, MD

... Many of these floppy infant disorders are shown ultimately to be genetically transmitted.

The floppy infant presents a diagnostic challenge to the attending physician. Enduring hypotonia, in isolation or associated with other clinical findings, is a serious sign and therefore merits a diligent and methodical search for its clarification; and since many of these floppy infant disorders are shown ultimately to be genetically transmitted, a carefully examined family pedigree and longterm follow-up of the affected infant becomes necessary.

The following commentaries and accompanying table briefly summarize some of the clinical and genetic features of the principal heritable disorders characterized by infantile hypotonia. These disorders are analyzed within the categories of autosomal dominant, autosomal recessive, X-linked, and non-Mendelian inheritance patterns and one disease from each of these categories is chosen for illustrative purposes.

Autosomal Dominant Disorders

About 10 to 20 per cent of infants with muscular dystrophy of the myotonic type show some hypotonia in the neonatal interval. They are born often after a pregnancy notable for polyhydramnios. Labor may be prolonged because of inadequate uterine contractions making these infants at high risk for perinatal asphyxia. The affected newborns display inadequate respiratory effort because of weak diaphragmatic and intercostal musculature. Assisted ventilation is then usually

required for several weeks. The principal clinical features in these dystrophic newborns include: (a) generalized hypotonia, (b) facial weakness with limited facial expression and poor suck, (c) joint contractures which are the result of in utero hypomobility, and (d) disturbed gastrointestinal function including swallowing difficulties, esophageal reflux, and delayed intestinal transit time. As in the case of adults with myotonic dystrophy, death is frequently the result of cardiomyopathy and cardiac arrhythmias. Congenital cataracts, however, are rare in the neonatal form of myotonic dystrophy. The respiratory weakness gradually resolves as overall muscle strength and swallowing improves.

A variable degree of mental retardation and learning disability are to be expected. These probably result from some neuroheteropic anomalies as well as the brain injuries caused by the perinatal asphyxia.

The diagnosis of myotonic dystrophy in a hypotonic newborn is strengthened by the examination of the mother. While unaware of her disease, she may show myotonia, demonstrated by an inability to relax her hand after a prolonged grasp. Electromyographic examination is often quite diagnostic with diminished resting membrane potential and repetitive depolarization (so-called dive-bomber phenomenon).

Autosomal Recessive Disorders

The heritable spinal muscular atrophies are a heterogenous group of disorders characterized by a biotrophic degeneration of motor neurons within the anterior horns of the spinal cord and in the motor nuclei of the brain stem. These degenerative changes in nerve cells, the basis for

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the hypotonia, cause a secondary skeletal muscle atrophy.

The spinal muscular atrophies may arise in adult life, adolescence, or in the newborn infant. Werdnig-Hoffman disease is the name given to the infantile form of which two varieties may be distinguished:

(1) The acute fulminating type which becomes clinically evident between birth and six months of age. In this acute form, the mother may have experienced diminished fetal movement during her pregnancy and typically the newborn is markedly hypotonic with the associated weakness more evident in the proximal musculature. Tendon stretch reflexes are diminished or absent. However, facial expression is preserved as are eye movements so that the infant appears alert and responsive. The tongue appears atrophic and fasciculations may be observed. Paradoxical respirations are often noted but respiratory function, for the moment, is adequate despite the generalized weakness. Most infants with the acute, fulminating form of Werdnig-Hoffman disease will succumb within six to twelve months because of an aspiration pneumonia facilitated by a diminished gag reflex and an ineffective cough.

(2) The infant with the chronic form of Werdnig-Hoffman disease typically appears normal at birth but develops some floppiness beyond the age of three months. The skeletal muscle weakness is more evident in the pelvic than in the shoulder girdle. The clinical course may stabilize for years with no evidence of progression. Joint contractures and scoliosis may become important management concerns as the infant grows older. Death in young adulthood is typically the result of progressive respiratory insufficiency.

The diagnosis of either variety of Werdnig-Hoffman disease is corroborated by muscle biopsy (which shows a neurogenic type of muscle fiber atrophy alternating with normally sized muscle fibers) and electromyography. Serum creatine phosphokinase is typically normal. Dicarboxylic aciduria has been identified in a few patients with Werdnig-Hoffman disease but its meaning is unclear.

X-Linked Disorders

The cerebro-oculo-renal syndrome [Lowe's syndrome] is a rare disorder associated with profound hypotonia and hyporeflexia of the newborn. These infants manifest the following additional signs during their short clinical course: cataracts, corneal lesions, glaucoma, a hypophosphatemic rickets of renal origin and severe

mental retardation. The mothers of these infants may have lenticular opacities, a partial expression of their carrier state. Later in infancy a renal tubular acidosis develops as well as an amino aciduria. Serum calcium is normal while serum phosphate is lowered and alkaline phosphatase elevated. Death from acidosis and renal insufficiency commonly occurs within the first few years of life.

Table 1. Heritable Disorders Associated with the Floppy Infant Syndrome*

Autosomal Dominant Transmission:

Achondroplasia
Central core myopathy
Congenital fiber-type disproportion
Congenital hypomyelinating neuropathy
Congenital myotonic dystrophy
Ehlers-Danlos syndrome [I, II, III, IV, VII, VIII]
Hereditary motor-sensory neuropathy
Marfan syndrome
Minicore myopathy
Myotubular myopathy
Nemaline myopathy

Autosomal Recessive Transmission

Acid maltase deficiency [Pompe's disease]
Amino acid dysmetabolism
Carnitine deficiency
Congenital fiber-type disproportion
Central core myopathy
Congenital muscular dystrophy
Congenital myasthenia syndrome
Ehlers-Danlos syndrome [VI]
Lissencephaly
Myophosphorylase deficiency [McArdle's disease]
Myotubular myopathy
Nemaline myopathy
Organic acid dysmetabolism
Peroxisomal disorders
Phosphofructokinase deficiency
Progressive degenerative diseases, various
Pyruvate dysmetabolism [Leigh's disease]
Spinal muscular atrophy [Werdnig-Hoffman disease]

X-Linked Transmission

Cerebro-oculo-renal syndrome [Lowe's syndrome]
Ehlers-Danlos syndrome [V]
Kinky hair disease [Menkes' disease]
Mucopolysaccharidosis [Hunter's disease]
Myotubular myopathy

Non-Mendelian Transmission

Chromosomal Aberrations
Down syndrome [trisomy 21]
Miller-Dieker syndrome [17 deletion]
Prader-Willi syndrome [15q deletion]
Cytoplasmic DNA Abnormalities
Mitochondrial myopathies

*Some listed diseases [eg, nemaline myopathy] have been associated with more than one pattern of genetic transmission and are accordingly placed in more than one category.

Non-Mendelian Genetic Disorders

A number of the floppy infant syndromes are associated with a demonstrable chromosomal abnormality, an example of which is the Prader-Willi syndrome (PWS). This disorder is said to occur about once in every 25,000 to 50,000 live births. The following features characterize PWS: hypotonia, early feeding problems, genital hypoplasia (undescended testes, small penis, hypoplastic labia minora, later amenorrhea) obesity, emotional instability and mental retardation. Over half of the cases identified as PWS have detectable abnormalities of the long arm of chromosome 15, best visualized during prometaphase banding. PWS inheritance may be multifactorial.

The diagnosis of PWS is often suggested in retrospect as the elements of the syndrome evolve. In infancy, the affected baby may appear lethargic and inactive, with profound feeding difficulties leading to a failure to thrive. The hypotonia tends to become less prominent over time and is supplanted by the characteristic central obesity, which becomes evident between six months and three years of life. Although language reception seems unimpaired there is a notable lag in speech. As the child becomes older, subtle dysmorphic features appear, including a narrow forehead (often associated with an underlying microcephaly), almond-shaped upslanting palpebral fissures, downturned mouth and small hands and feet. Intellectual impairment and behavior problems, particularly food hoarding, are encountered in the school-aged child with PWS. Hypothalamic dysfunction is the basis for the hypogonadism and ultimately for the short stature seen in the PWS children.

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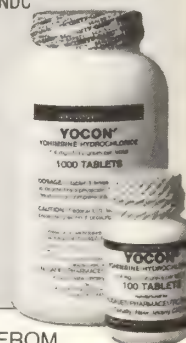
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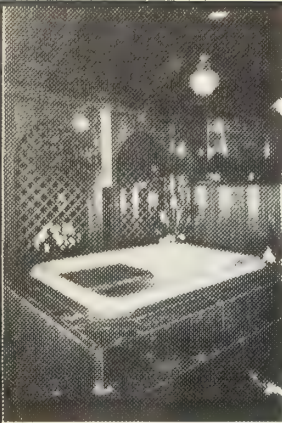
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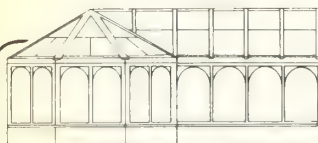
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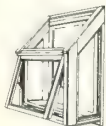
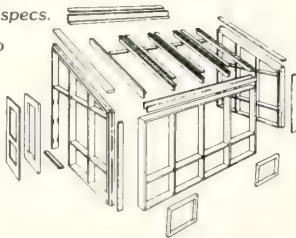
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Diagnosis and Management of Diseases Affecting the Motor Unit in Infancy

Henry C. Maguire, MD
John T. Sladky, MD

... Hypotonia can result from numerous disorders affecting the brain, the neuromuscular system, or both.

The floppy infant is a challenging diagnostic problem for the pediatric neurologist because the clinical phenotype, the hypotonic infant, can result from numerous disorders affecting the brain, the neuromuscular system or both. This discussion will deal with the more important diseases in which hypotonia is associated with weakness due to involvement of the motor unit in infancy.

The motor unit is comprised of the anterior horn cells of the spinal cord, the peripheral nerve, the neuromuscular junction and the muscle. Table I lists diseases affecting each portion of the motor unit which cause floppiness in infancy. Before discussing the diseases individually some general comments should be made concerning clinical findings and diagnostic tools used in the assessment of the hypotonic infant.

Infants are floppy because of decreased muscle tone. They have the feel of a rag doll. Spontaneous movements are usually present but are limited in vigor. There is decreased resistance to passive movement and usually increased range of joint motion. Because of the decreased tone the limbs will often assume abnormal postures. For example, the legs will lie externally rotated

and abducted, a position likened to a "frog's leg" posture. Two maneuvers are useful in demonstrating decreased tone. When the infant is suspended with the examiner's palm underneath the chest, the patient's head, arms, and legs hang limply forming an inverted "U" posture. When the child is brought from a supine to sitting position by applying traction to the arms, the head lags behind the rest of the torso and falls forward when it reaches the vertical axis.¹

Serum muscle enzymes, nerve conduction studies, electromyography, and tissue biopsy are important laboratory tools in evaluating diseases of constituent elements of the motor unit. Elevations of creatine phosphokinase and aldolase in the serum generally reflect damaged or degenerating muscle tissue and suggest that the primary process is myopathic. Electromyography (EMG) can be confirmatory when hypotonia and weakness are due to neuromuscular disease and are not central in origin, indicating the cause as either myopathy or denervation. Nerve conduction studies (NCS) can help to identify whether the peripheral nervous system is affected and whether the primary process is axonal degeneration or segmental demyelination. Muscle or nerve biopsy have become increasingly important diagnostic tools with the application of histochemistry, immunostaining and biochemical and molecular biological techniques.

Anterior Horn Cell Disease

Werdnig-Hoffman disease is the only infantile, non-infectious disorder in which motor neuron impairment causes hypotonia and weakness. The clinical presentation is fairly characteristic. Decreased motor capacity at birth or early infancy

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is often the presenting complaint to the pediatrician or pediatric neurologist. Children typically develop feeding difficulty with poor suck and swallow, respiratory embarrassment and occasionally failure to thrive. A history of decreased fetal movements can be elicited from the mother in approximately thirty per cent of the cases,² presumptive evidence that degeneration of motor neurons began antenatally.

Certain clinical features suggest involvement of the peripheral nervous system. Because there is a loss of motor axons the efferent portion of the myotatic reflex arc is lost and reflexes are severely depressed or absent. Hypotonia is accompanied by varying degrees of muscle weakness depending on the stage of the disease. Hypotonia and weakness of the legs leads to abduction and external rotation of the hips. Sensation is intact and the child grimaces and cries to noxious stimuli. Involvement of bulbar motor neurons eventually results in fasciculations of the tongue and orbicularis oculi. A common observation in these children, however, is their bright, lively facial expressions despite severe somatic weakness. This is in contrast to some hypotonic infants whose facial expressions and affect appear depressed. Once the diagnosis is suspected an EMG/NCS should be performed. Electrophysiological testing may confirm denervation in muscles while demonstrating normal sensory nerve conduction, thus indicating that the pathological process is proximal to the level of the

dorsal root ganglia and is not a peripheral neuropathy. A muscle biopsy will typically show neurogenic changes with groups of small atrophic myofibers adjacent to large fibers.

The prognosis is poor. Patients who present in the first three months of life frequently succumb to pneumonia or respiratory failure by no later than two to three years.³ Therapy is supportive with particular attention to pulmonary toilette for the patient and genetic counselling for the parents. Gastrostomy may be necessary if the patient is too weak to feed.

Peripheral Nerve Disorders

Peripheral neuropathies are uncommon in infancy. They can, however, cause hypotonia and therefore need to be considered in the differential diagnosis of the floppy infant. Infantile hypotonia can be considered in three groups: 1) hereditary sensory motor neuropathies (HSMN), 2) acquired demyelinating neuropathies, and, 3) miscellaneous disorders.

The hereditary sensory motor neuropathies represent a diagnostic category defined by Dyck and colleagues.⁴ They are both phenotypically and genotypically heterogeneous. Some are transmitted as autosomal dominant and some as recessive traits. HSMN types I and II (the demyelinating and axonal forms of Charcot Marie Tooth disease) are dominantly inherited and are rarely symptomatic in infancy. Typically, they present in the late first or early second decade with a foot drop, pes cavus, and hammer toes. Nerve conduction studies can usually characterize the type on the basis of conduction velocities. Diagnosis is confirmed by demonstrating similar electrophysiological abnormalities in one of the child's parents establishing a dominant pattern of inheritance.

HSMN type III (Degerine Sottas disease) is another inherited neuropathy that usually presents before twelve months of age. Hypotonia is a prominent symptom in two-thirds of cases along with delayed motor development.⁵ The weakness, in general, is more severe than in other types of HSMN and there are case reports of transient respiratory failure. The disease is inherited in an autosomal recessive fashion and there is usually no family history. Nerve conduction studies reveal severe slowing of conduction velocities. Unless one can demonstrate an affected sibling and normal parents, the phenotype of HSMN III can be indistinguishable from children with hypomyelinating neuropathy.⁶ Nerve biopsy is helpful in distinguishing these

Table 1. Diseases of the Motor Unit Causing Hypotonia in Infancy

Anterior Horn Cell
Werdnig - Hoffmann disease
Peripheral Nerve
Guillain-Barre syndrome
Chronic inflammatory demyelinating polyneuropathy
Congenital hypomyelination syndrome
Hereditary sensory motor neuropathy
Dejerine Sottas neuropathy
Neuroaxonal dystrophy
Giant axonal neuropathy
Neuromuscular Junction
Neonatal myasthenia
Congenital myasthenia
Acquired Myasthenia gravis
Botulism
Muscle
Congenital muscular dystrophies
Inflammatory myopathies
Congenital myopathies
Mitochondrial myopathies
Metabolic myopathies/storage diseases

entities. The most characteristic feature of HSMN III is prominent onion-bulb formations indicating repetitive segmental demyelination and remyelination.

Chronic inflammatory demyelinating polyneuropathy (CIDP) has only been recently described in infancy and is important to recognize because it is potentially treatable. One-third of patients with CIDP in early childhood were hypotonic in the newborn period with generalized weakness and hypoactive reflexes.⁷ The cerebrospinal fluid protein was elevated in these patients and there was no family history of a neuropathy. Nerve conduction studies revealed marked slowing consistent with a demyelinating neuropathy. In half of these children specific electrophysiologic features of acquired demyelination: multifocal slowing, conduction block and temporal dispersion, were present.⁷ Sural nerve biopsy was also helpful in establishing the diagnosis typically demonstrating prominent edema and inflammatory changes with only rudimentary onion-bulb formation.

Accurate diagnosis is important because these patients respond to steroids with improvement of the weakness and hypotonia.⁷ Sometimes the clinical and laboratory data do not allow for a definitive diagnosis of an acquired demyelination disorder. In instances with a progressive demyelinating neuropathy and no family history, a therapeutic trial steroids is appropriate.

The third group of peripheral neuropathies in infancy causing hypotonia are characterized by specific morphologic features of nerve or muscle including neuroaxonal dystrophy, giant axonal neuropathy, and congenital hypomyelinating neuropathy. These disorders are rare.

In neuroaxonal dystrophy most patients are normal until after six months of age when they develop progressive hypotonia, weakness, and muscle atrophy along with disturbed extraocular movements. Nerve conduction studies and EMG are normal early in the disease. The diagnosis is established by examination of the sural or intramuscular nerves which demonstrate spheroidal axonal swellings. These spheroids, ultrastructurally, are composed of glycogen, mitochondria, dense bodies and membrane-bound vesicular profiles.^{8,9} Inheritance is autosomal recessive.

Giant axonal neuropathy (GAN) is a chronic distal sensorimotor neuropathy that seldom presents in the first year of life. There have, however, been case reports of hypotonic infants with morphologic features consistent with this diagnosis, including eosinophilic axonal spheroids due

to dense accumulations of neurofilaments within the central axoplasm.^{10,11} The disease is inherited in an autosomal recessive fashion and has the curious clinical feature of hypopigmented, curly hair in the majority of patients.

Congenital hypomyelinating neuropathy usually appears in the first months of life with hypotonia, areflexia, distal muscle weakness, and atrophy. The diagnosis is suspected when nerve conduction is slowed. The disorder is not easily distinguished from other demyelinating neuropathies of infancy. Nerve biopsy is essential in establishing the diagnosis and reveals relative sparing of large caliber axons and a primary failure of normal myelination, in contradistinction to HSMN III and CIDP in which there is segmental demyelination and remyelination.⁶ The prognosis in these disorders is poor with the majority of reported cases succumbing in infancy. Survivors have delayed motor development though some eventually do walk.

Disorders of the Neuromuscular Junction

At the neuromuscular junction (NMJ) a motor nerve action potential causes the release of acetylcholine which diffuses across the synaptic cleft and binds to the specific receptor on the muscle membrane. This in turn results in the depolarization of the muscle fiber membrane and release of calcium from the sarcoplasmic reticulum followed by contraction of the muscle fiber. Acquired or congenital defects at the NMJ may cause hypotonia in infancy.

Myasthenia gravis is an autoimmune disease that results in ptosis, dislopia, and generalized weakness in adults. It is caused by IgG antibodies directed against post-synaptic acetylcholine receptors at the NMJ. Antibody-mediated destruction of acetylcholine receptors impairs transmission of nerve impulses to muscle fibers.

Because IgG crosses the maternal placental barrier a transient immunologically-mediated disease may arise in infants born to myasthenic mothers. This condition is known as neonatal myasthenia gravis (NMG). Infants with NMG are hypotonic, weak, have a soft cry, and may develop respiratory failure. Occasionally, they exhibit ptosis and ophthalmoplegia. While two-thirds of these children are symptomatic within several hours after birth some appear well until day three.¹² The diagnosis should be suspected in a floppy infant whose mother has myasthenia gravis. The severity of the maternal disease is not predictive of the gravity of symptoms in the child. Overall, approximately 15 per cent of children

born to myasthenic mothers will develop NMG.

Once suspected, the diagnosis is confirmed electrophysiologically by demonstrating a typical decrement in the amplitude of the compound motor action potential during repetitive motor nerve stimulation. Alternatively, clinical improvement after administration of edrophonium or neostigmine is highly suggestive of the diagnosis of NMG. Both medications are acetylcholinesterase inhibitors and improve neuromuscular transmission by slowing the enzymatic hydrolysis of acetylcholine in the NMJ. In cases that do not respond to anticholinesterases, plasma exchange therapy, which reduces the amount of circulating anti-receptor antibody, can be effective.¹³ The duration of the illness is usually two to six weeks.

Congenital myasthenia gravis is characterized by an abnormality in the structure or function of part of the neuromuscular junction. There is no distinct clinical phenotype among these disorders but they can present as weakness and decreased tone in the first months of life. Both autosomal dominant and recessive transmissions have been documented in some pedigrees. The types of defects described under the general heading of congenital myasthenia include acetylcholinesterase deficiency, abnormal synthesis or mobilization of acetylcholine, paucity of secondary synaptic clefts, and prolonged opening of acetylcholine receptor-coupled ion channels.¹⁴

Botulism is a recently recognized cause of hypotonia and weakness in infancy and is important to recognize because of the need in such cases for supportive feeding and respiratory care. When *Clostridium Botulinum* spores germinate in the intestine the elaborated botulinum toxin is absorbed systemically. Botulinum toxin, the most potent neurotoxin known to man, prevents the release of acetylcholine from the presynaptic terminals of motor axons. This blocks transmission of nerve impulses at the NMJ and results in paralysis of both striated and smooth muscle. The clinical consequences are hypotonia, weakness, areflexia, constipation, limitation of extraocular movements, and sluggishly reactive pupils. Once suspected, the diagnosis can be proven electrophysiologically by: (1) an increment of the compound motor action potential following repetitive motor-nerve stimulation at high rates (20 HZ or greater), (2) voluntary motor units that are short in duration and decreased in amplitude, and, (3) fibrillations and positive sharp waves at rest on EMG.¹⁵ Definitive diagnosis rests on the isolation of the organism or toxin from the stool.

The age of onset is usually 7 to 14 weeks with 94 per cent of patients younger than six months of age.¹⁶ Over one-half of the reported cases in the United States were from California, Utah, or Pennsylvania. It is interesting that in 12.8 per cent of cases of sudden infant death syndrome *C. difficile* toxin was isolated from the stool, suggesting a possible link between the two disorders.¹⁷

Care is supportive with careful attention directed towards protecting the airway because of pharyngeal weakness. Because of weak sucking and swallowing infants frequently require nutritional support in the form of nasogastric feedings. In severe cases, affected infants may require mechanical ventilation for several weeks. In virtually all cases there is slow recovery of strength over days to weeks as toxin-inactivated NMJs degenerate and new NMJs are formed. Residual deficits are uncommon. Cases of recurrent infantile botulism are rare but have been reported.¹⁸

Muscle Disorders

Any disease affecting muscle in infancy may cause hypotonia. The disorders involving muscle in the newborn period include: (1) congenital muscular dystrophy, (2) polymyositis, (3) congenital myopathies, (4) mitochondrial cytopathies, and (5) metabolic myopathies. Except for congenital myotonic dystrophy, the diagnosis requires histopathologic and biochemical analysis.

Infants with congenital muscular dystrophy are weak and hypotonic at birth. Arthrogryposis, hip contractures, and hip dislocations are common. Serum muscle enzymes are only mildly elevated and EMG reveals small amplitude polyphasic motor units with a myopathic recruitment pattern. Loss of myofibers, with fatty and connective tissue infiltration, is present on biopsy. Other clinical and laboratory features help differentiate different subtypes of congenital muscular dystrophy. In the Fukuyama type, seen predominantly in Japan, mental retardation is common and muscle weakness is progressive with death usually before ten years of age.¹⁹ Brain imaging studies disclose cerebral hypomyelination, polymicrogyria, lissencephaly, and cortical heterotopia.¹⁹ The spectrum of congenital muscular dystrophy described in North America and Europe differs clinically from the Fukuyama type. Some children have a relentlessly progressive lethal course. In others, however, motor milestones are gained, albeit slowly. Intelligence is usually normal and survival into adulthood the

rule. Brain abnormalities are rarely demonstrated radiographically. The inheritance pattern in most forms of congenital muscular dystrophy is autosomal recessive but autosomal dominant inheritance is described.²⁰

Polymyositis rarely occurs in infants. It is a potentially treatable disease and should be considered when evaluating the floppy infant. These patients present with proximal or generalized muscle weakness, hyporeflexia, and hypotonia. The diagnosis is suspected when there is marked elevation of serum CPK. The EMG is myopathic while nerve conduction studies are normal. Muscle biopsy can be nonspecifically abnormal or show typical findings of polymyositis: myofiber degeneration and regeneration, perifascicular atrophy and inflammatory infiltrates. Differentiation from congenital muscular dystrophy can sometimes be difficult particularly when the muscle biopsy is not diagnostic. Infants with polymyositis, in contradistinction to congenital muscular dystrophy, respond well to treatment with corticosteroids.²¹ Therefore, it is reasonable to consider a therapeutic trial of steroids in an infant with a sporadic myopathy and an elevated CPK when the biopsy is not specific.

The congenital myopathies represent a group of disorders which are characterized by specific changes present on histochemical or electron microscopic examination of muscle biopsy specimens. Floppiness from birth is a common clinical feature in some but not all cases. These patients often have accompanying ptosis and facial weakness, a high arched palate and dislocated hips. Motor development is delayed and occasionally there is cognitive delay. Unlike other primary diseases of muscle, such as muscular dystrophy or polymyositis, there is little or no elevation in the plasma CPK but the EMG demonstrates myopathic motor unit potentials and recruitment. Congenital myopathies may be inherited in an autosomal dominant, recessive or x-linked fashion while sporadic cases also occur.

Over ten different types of congenital myopathies have been identified and they are named after their primary morphological features. For example, in central core disease when muscle fibers are stained for oxidative enzymes there is absence of staining in the center of the fiber. In patients with centronuclear or myotubular myopathy the nuclei of the myofibers are located centrally and not peripherally along the subsarcolemmal membrane as is seen in normal, mature muscle cells.

Congenital myotonic dystrophy presents in the

newborn period with generalized hypotonia, pharyngeal and generalized muscle weakness, often with feeding and respiratory difficulties. These infants often have marked temporallis muscle wasting, anteversion of the philtrum, and tenting of the upper lip. In some series anal sphincter insufficiency is reported.²² Muscle biopsy in these infants does not show any specific features. The disorder is inherited in an autosomal dominant fashion and in virtually all cases of congenital myotonic dystrophy the affected parent is the mother. The reasons for this pattern of inheritance are not clear. Thus, features consistent with myotonic dystrophy in the mother virtually confirms the diagnosis in the affected newborn. In most reported cases of congenital myotonic dystrophy the mother was undiagnosed at the time of delivery and was discovered to have myotonic dystrophy only as part of the evaluation of her floppy newborn.²²

The treatment for congenital myotonic dystrophy is supportive. The profound weakness present in the perinatal period, which may even require ventilatory support, is transient and gradually improves within days to weeks but occasionally may persist for months. The overall outlook for these infants is guarded because in addition to their neuromuscular disease many infants with myotonic dystrophy will be mentally retarded.²³

Abnormal mitochondrial function results in a variety of clinical syndromes some of which arise in infancy. Newborns with mitochondrial encephalomyopathies typically present with generalized hypotonia, seizures, and developmental delay. Serum levels of lactate pyruvate may be elevated reflecting disordered mitochondrial metabolism. The EMG is myopathic. Definitive diagnosis is made by muscle biopsy when subsarcolemmal accumulations of mitochondria are demonstrated. In the mitochondrial cytopathies there are defective respiratory chain enzyme systems within the mitochondria disturbing the formation of ATP via oxidative phosphorylation. It is often possible to identify the specific enzyme defect and in certain situations institute effective treatment with agents that bypass the metabolic blocks within the respiratory chain. Occasionally maturation of the enzyme systems is delayed and weak hypotonic infants can, with supportive care, become normal over a period of months to years as the enzymes become functional.²⁴

Enzyme deficiencies can cause abnormal glycogen metabolism leading to infantile hypotonia. Acid maltase deficiency, otherwise glycogenosis

type II or Pompe's disease, manifests in the newborn period with generalized weakness, hypotonia, macroglossia, and organ enlargement. Death, due to cardiac or respiratory failure, occurs in the first or second year of life.²⁵ CPK can be mildly elevated and the EMG is noted for the presence of myopathic units and electrical myotonia in infancy. Muscle biopsy demonstrates glycogen vacuoles within myofibers. There is no effective treatment. Branching enzyme deficiency, glycogenosis type IV, is clinically similar to acid maltase deficiency. In both disorders the diagnosis is established by identification of the specific enzyme defect in cultured white blood cells or fibroblasts.

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SPEAK UP AMERICA
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Therapy and Rehabilitation of the Floppy Infant

Gloria D. Eng, MD

Even with support, some families cannot cope with a terminally ill child in the home and hospice care or even hospital care will be needed.

Even the most hapless infant who lies immobile, too weak to suck and swallow, who whimpers instead of cries, whose life-span appears predictably short, deserves that life to be as near normal as possible and free of discomfort. (Fig 1 & 2)

Therapy in the infant with a neuromuscular disorder is based (whenever possible) on an accurate diagnosis. Knowing the natural evolution of the disease process and its associated complications helps in practical management. The principles of rehabilitation remain the same for the child with a shortened life-span and for the one who grows into adulthood; that is, (1) One should try to elicit sequential development — bring out the best possible mental, emotional and physical capabilities as the child grows; and (2) Prevent secondary complications and deformities which would impair comfort.

The most common diagnosis to be considered in the floppy baby is Infantile Spinal Muscular Atrophy (Type I, Werdnig-Hoffmann Disease or SMA). Though this disorder rarely allows the infant to survive beyond three years of age (the mean survival in our series is between seven and eight months¹), counsel and support are given

the parents in understanding the diagnosis and helping them develop a level of comfort in nurturing, feeding and moving their infant.

Feeding

Breast-feeding may be difficult because the infant tends to fatigue quickly and does not empty the breast. The infant may not extract enough to sustain a good nutritional level. Invariably bottle feeding supplants breast-feeding and then the choice of adequate nipples must be tried and selected such as the premature baby's nipple with a large opening. Passively pursing the infant's lips by supporting the buccinators with slight forward thrust of the jaw may provide improved suck. Small, frequent feeds are necessary because the baby fatigues easily. Body weights should be recorded as a guide to the efficacy of nutrition. This can aggravate the already weakened state of the child. Continuous nasogastric tube feedings are sometimes necessary, but bolus feedings should be avoided because the latter may encroach on excursion of the diaphragm. Percutaneous gastrostomy can be considered in older infants when nasogastric feedings are impractical. Constipation can be a problem and should be managed with Malt-supex and glycerine suppositories and massage of knees against the abdomen. This will lessen the effects of constipation on respiratory effort.

Positioning

Holding and positioning of the floppy infant requires deftness and imagination. Babies who have normal muscle tone cling to their mothers and

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there is a reciprocal situation of holding on to each other. In the floppy infant, the caretaker has to provide total support. This becomes more difficult as the child grows larger. Control for the head, trunk, and extremities must be provided because the infant has a tendency to develop deformities such as torticollis, scoliosis, contractures of the hips in abduction and external rotation, knee flexion contractures and ankle deformities in varus or valgus deviation.

Positioning in an appropriate seat is necessary for comfort and good alignment. A foam contoured seat can be devised or an infant seat can be adjusted with side-padding or wedge, a cut-out ring for the occupant, and straps to secure the infant in the semi-reclined position. A plinth made out of felt or foam, scooped out to cradle the head and buttocks and attached with velcro straps may be helpful. A small hammock allows gentle movement and cradles the child in a comfortable position. In the supine position small wedges or rolls prevent the hips from turning out into the so-called pithed-frog posture. In side-lying, a bolster or towel roll placed against the back affords the infant some support. Side-lying allows the infants' hands to come to midline and appropriate light-weight toys should be available for him to explore with his hands and mouth. At five-six months a bolster can be placed under the flexed knees against the buttocks to bring the feet up towards the abdomen and allow the hands to explore legs and feet. Prone-lying over a small wedge or bolster stretches the upper extremities and allows attempts at head extension. However, most infants with SMA or other neuromuscular disease do not tolerate that position, because of respiratory compromise.²³

Even the most hapless infant. . . deserves that life to be as near normal as possible and free of discomfort.

Exercises

According to Vignos⁴, it is important to "maximize muscle function and reduce secondary crippling deformities." He discusses the need for exercise as it relates to individuals with Duchenne muscular dystrophy or other neuromuscular disorders, but the principles apply equally well to the floppy infant — especially the one who grows up past infancy. There is need to maintain maximum strength within the limits of the disease process and prevent disuse atrophy and contractures around the weight-bearing joints. Thus,

judicious exercises as advocated by Boehme⁵ can facilitate improved head, trunk and hip girdle control; afford mobility by assisting rotation of the trunk; and, permit normal postural alignment. Gentle stretching of the shoulders, elbows, wrists, hips, knees, ankles, and spine should be done at least one to two times daily with slow, sustained stretches following bathing or diapering. Even the weakest child seems to tolerate this handling and shows at least transient improvement in strength. For the infant with only mild to moderate weakness, the exercises recommended by Levy⁶ can be useful. Dynamic, high resistive exercises are beneficial according to Fowler⁷ if (1) degree of weakness is not severe; (2) rate of progression remains relatively slow; (3) rate of increasing intensity of exercise is slow; and (4) the exercise period is of limited duration taking into consideration the individual's other daily physical activity. A concept to be remembered in the care of the floppy child is to minimize bed rest and inactivity during intercurrent illness to prevent precipitous loss of strength following immobilization.



Fig. 1. Hypotonic infant. Note inability to extend head and flaccidity of limbs.

Orthopedic Considerations

In the very fragile infants such as those with SMA, congenital dystrophies, and myotonic dystrophy, intrauterine immobility has resulted in changes in bone formation. Rodrigues⁸ has described thinning of the shafts of the long bones, some with fractures at the growthplates, periosteal bone reactions, and thinning of the ribs. Some of these infants have clubbed feet because the plantar flexors and invertors of the ankle are stronger than evertors and dorsiflexors and these deforming forces, coupled with immobility, result in fixed contractures. Some infants with SMA at birth can even be confused with those with osteogenesis imperfecta.⁹ These infants must be exercised with great caution. Well-fabricated, light-weight plastic splints can hold hands and feet in good position and allow for fracture healing as well as prevent new or further deformity.

Besides deformities of the feet and ulnar drift of the hands, dislocation of the hips is a common phenomenon in the floppy infant. Orthopedic consultation is necessary to provide abduction splints and later when surgical intervention may be needed.

Unilateral dislocation of the hip is a particular problem because of resulting pelvic obliquity and the initiation of a lumbo-sacral scoliosis. Positioning and exercises in this situation must be precise and should include, when possible, stretching of the muscles attached to the pelvic brim and mobilization of the spine, and strengthening of the paraspinal muscles against gravity.

Respiratory Care

Suctioning of the oropharynx in the small infants prior to feeding may be necessary. This can be

done with a small bulb syringe or through a catheter with suction provided by a portable battery-charged apparatus. Later, a standard suction machine may be required in the home for regular "deep" suctioning. Chest physical therapy, including percussion, postural drainage, and facilitated cough should be taught to the parents for use in case of pulmonary congestion or infection. In the care of a child who is expected to survive the period of infancy, aggressive intervention is indicated to include prophylactic antibiotics, the use of bronchodilators coupled with intermittent positive pressure devices, and use of oxygen during acute respiratory distress. Intubation with total respiratory assist may also be a consideration for an infant with reversible processes such as pulmonary infection and atelectasis. In the event of respiratory failure, the use of positive or negative breathing device should have been discussed with the family long before the need arises. Even on a respirator, the infant with SMA I can hope to live only a few extra months.¹⁰ All children with severe, infantile neuromuscular disorders can be expected to develop restrictive lung disease and ineffective coughs. It is important to maintain mobility of the chest wall, to prevent spinal curvatures, to strengthen and support their abdominal musculature and teach them breathing exercises. It is of interest to note that even in the infant with SMA I, the diaphragm is usually spared the effects of neurogenic disease and can remain an effective bellows.

General Care Considerations

Total care of the floppy infant has to be shared by a number of persons. Home nursing, home health aides are integral to the delivery of care to alleviate the inevitable exhaustion of the parents, particularly the mother. Even with support, some families cannot cope with a terminally ill child in the home and hospice care or even hospital care will be needed.

Some special concerns arise for floppy infants with other diagnoses. The infants with myotonic dystrophy, especially the infantile form, besides hypotonia, have pharyngeal weakness, and occasionally, bradycardia and cardiac conduction defects. They also present with severe pes equinovarus deformities and hip dislocation. Unlike the winsome and responsive facies of the SMA I infant, this child has a long myopathic facies and frequent extraocular palsies. The infant with congenital muscular dystrophy also presents with a myopathic facies and may have mild to severe weakness. This infant is susceptible to unex-



Fig. 2. 5 months old with infantile spinal muscular atrophy lying in a typical hypotonic posture.

pected infant death and must be monitored closely.

Myopathies, such as fiber type disproportion, nemaline, central core or centronuclear myopathies can present a better prognosis. Most of these children grow up and improve in muscle strength and function. The child with nemaline myopathy may be mildly floppy during the first few years of life, but is at risk for respiratory infections. Central core disease may present in a child who is severely weak or only mildly affected. Orthopedic problems include pes equinovarus, hip dislocations, patellar dislocations, scoliosis and, not to be forgotten, the propensity to the complication of malignant hyperthermia when under anesthesia.^{11, 12} The mitochondrial myopathies may affect a child mildly or globally, including the central nervous system. Control of seizures may be necessary in some of these infants.

Some of these infants progress to childhood and adulthood and will require ongoing rehabilitative intervention. Orthotic needs include: bracing for weak ankles in the form of articulated ankle-foot orthoses, long leg braces to control hips, knees and ankles with or without reciprocating attachments, the use of body orthoses in an effort to hold the spine as straight as possible until time for spinal stabilization and fusion. Standing frames and mobility devices are recommended for certain children.² Careful evaluation of educational capabilities and fostering of adequate placement in the school system should be addressed by the health care provider. The psycho-social issues in the care of the floppy infant and the older children with neuromuscular disorders are crucial and require a sensitive, skilled and coordinated effort.

Anticipatory rehabilitation demands an orchestrated effort by a great many professionals, the parents, and the child himself in order to achieve an optimal outcome.

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Parenting a Floppy Infant

Martha Susan McDonald, ACSW, CISW

My own child. . . was so weak at birth that she couldn't even cry, yet I cried for weeks.

Family life changes and readjusts with the birth of each new child. When the new baby is a floppy infant, however, an atmosphere of crisis develops and the adjustments are immense. My own child, a third girl, was so weak at birth that she couldn't even cry, yet I cried for weeks. There followed a long period of seeking strength and purpose to meet the unfolding demands of caring for a floppy infant. Initially, I experienced the crisis as a loss of personal and parental power and control as I found myself nurturing a human being who, at first, offered me little or no response. I found that caring for a weak child required a great deal of maternal strength.

Alexandra's birth four years ago was by caesarian section at the John Dempsey Hospital, Connecticut, where I had worked in Pediatrics as a social worker. When the incision was made the placenta was lacerated. Since Alexandra was lodged in a jackknife position, the physician had to remove the placenta rapidly and pull her out. The umbilical cord then ruptured and we both lost a great deal of blood. Alexandra was resuscitated immediately but required oxygen and a plasma and blood transfusion. Only gradually was she weaned from the ventilator support and oxygen, as I daily watched and waited for her recovery from stupor. Her severe hypotonia was to remain for months, but after 14 days she was transferred from the Neonatal Intensive Care

Unit to the newborn nursery for three more days where I continued to struggle to learn how to feed her. At first she was tube fed, but gradually she was advanced to bottle and breast feeding over a two month interval. Slowly she grew stronger yet her hypotonia persisted. At three years of age she was diagnosed as having a Prader-Willi Syndrome.

Parents prepare for a new child while growth occurs in utero. During the prenatal period there is time to fantasize about its gender, how the child will look, how it will fit into the structure of the existing family, and how that child will grow, develop and contribute to the family. After Alexandra was born all of these dreams were shattered, and my focus of attention totally shifted. I wondered not what she might become, but whether she would even survive. It was a time when her excruciatingly slow movements contrasted sharply with the intense and alert activity of the hospital world around her. The medical staff was constantly working on her, and my level of anxiety stayed especially high while she remained in stupor. She needed blood, oxygen, sustenance — total support to live. Alexandra was in such marked contrast to my anticipations that, though she lived, I grieved the loss of our "normal" child. In fact, when the neurologist told us that she was going to live, we were paradoxically devastated. Denial was now impossible, and the enormity of the problems which lay ahead now had to be faced.

We needed the help of the medical staff to get through the barriers around our baby. We were fighting not only the rejection we personally felt toward our baby, but also the frightening tubes and wires surrounding her and making her untouchable. When shown how to parent in this

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new and frightening setting, I felt more at ease and more effective. I regret that it took me four days to learn how to change my baby's diaper. But it was a relief to learn that I could indeed put my hands in the isolette, hold a thermometer in place, and bring some comfort to Alexandra.

The feeding of my hypotonic infant was particularly difficult, because she was unable to breast feed or even bottle feed. When attempting to feed, she tired quickly and was alert for only limited periods of time. I wanted desperately for her to be mine, to hold her and feed her as I had my other children. The doctors helped me when they clarified my child's needs and showed me which of her needs I could best meet. Tube feeding became necessary in order to conserve her strength and build herself up. The staff instructed me in gavage feeding, and I was able to practice and be checked in a supportive setting at the hospital. I was encouraged to then hold and talk to my baby, an emotional substitute for the normal interaction of nursing my baby.

The feeding of my hypotonic infant was particularly difficult because she was unable to breast feed or even bottle feed.

After clearly establishing the needs of my child and how I could help provide for these needs, I required some private space and time to carry out these responsibilities. The hospital has a family room that I felt was ours. Here I could just hold my infant, her sisters and other relatives could join me and we could begin feeling at home with our baby. This early preparation was essential. It provided me with some semblance of how it would feel to be in charge, while all the modes of support I knew to be available were still close by. Occasionally a nurse would come by to offer support. I felt most in control there and could begin to enjoy my baby, to touch her, to watch her, to have her lie on my stomach. For me these were the first moments in which I experienced the joys of being Alexandra's mother.

Finally, in planning the discharge, a schedule for medical support at home became essential. A referral to the visiting nurses and an early intervention program helped me to know that I was not alone, nor would I be alone for a long time. Furthermore, I needed to accept that even though a re-hospitalization would be likely, it did not mean failure. It is important for the medical staff to communicate this idea because the fears of

returning to the hospital may have led to pushing our baby too hard and too soon.

In retrospect, it would have been helpful if someone had been able to aid us in exploring what our family resources were, and how we had dealt with crises in the past. We might then have been more able to focus on the positive approaches to our situation and minimize those responses which were ineffective or negative. It requires a sensitive nursing and social work environment to support the parents in their normal grieving process, and then to help them get past their feelings of anger and guilt. Sometimes I found myself angry with the specialists who are concentrating on the elements of diagnosis and prognosis while I was concerned with the dimensions of my child's current dependence and the stability of our family life. A special glimpse of the future that the hospital did provide was found in the pictures of neonatal "graduates" in a collage on the hospital wall. I happened upon them one day and felt a positive surge of hope.

Coping with my floppy infant at home was a major challenge. After bringing Alexandra home, feeding was my most anxiety ridden nurturing activity. I feared that she would not get enough food to grow. I feared, too, that she might choke or somehow be harmed while being tube or bottle fed. Although Alexandra couldn't demand vocally, the household nevertheless revolved around her needs. Our other children struggled for attention and reassurance. Fortunately, our extended family supported us in parenting all of our children, and though they were not comfortable in the feeding of Alexandra, we eventually were able to leave the house for short periods of time with their encouragement.

In retrospect, it would have been helpful if someone had been able to aid us in exploring what our family resources were, and how we had dealt with crises in the past.

Though the beginning of life with a floppy infant requires tremendous adjustment and effort, many of these affected children eventually contribute to the family, and the initial struggles are rewarded many times over. My daughter now gives so much back to me. Yet, I realize that without the support of the medical staff, I might not have made it through that early period to enjoy the pleasure she provides for me today.

Based upon my own experience, I recommend the following suggestions for medical personnel working with families with a floppy infant:

1. Be aware that these families are in crisis and are grieving. Listen to their feelings of denial, anger, depression and gradual acceptance.

2. Assess the medical situation and the capabilities of each family member, and then attempt to define each individual's role in supporting the affected infant. Encourage the entire family to help in the daily care of the infant and have each member personally experience the infant's struggle for survival.

3. Help the family to accept its differences, to develop patience and to unite in purpose and resolve. Help from extended family and friends is essential.

4. Help the family members as they search for a stable way of living. Be aware that the family is concentrating upon the moment and the immediate needs for the infant's survival rather than on the future and what the diagnosis, and its implications, might be.

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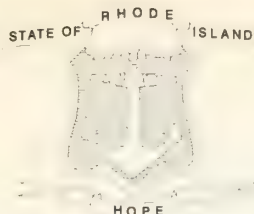
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Breast Cancer in Rhode Island

Breast cancer is a serious disease of women in Rhode Island. In 1987, 707 new malignancies of the female breast were reported to the Rhode Island Cancer Registry, and 199 Rhode Island women died of the disease, accounting for 4.1 per cent of all deaths among resident Rhode Island women that year.

Breast cancer incidence rose an estimated 44 per cent in the US between 1950 and 1985 (Figure 1). Although comparable trend data are not available for Rhode Island, its experience was probably similar to neighboring Connecticut's, where breast cancer incidence rose 61 per cent between 1935 and 1979. In contrast, breast cancer mortality remained stable in the US and Rhode Island between 1950 and 1979. The disparity between incidence and mortality trends may have been caused by improvements in screening, treatment, and access to both. Breast cancer mortality in Rhode Island, as in other urban areas of the US, has been consistently higher than breast cancer mortality in the nation as a whole; the cause of this differential is unknown.

Rhode Island breast cancer death rates are higher among black women than white women (Figure 2). In the US death rates are about equal between races, but incidence rates are lower for black women than white women. These data suggest that black Rhode Island women may have insufficient access to breast cancer screening and treatment.

Recent consensus recommendations for breast cancer screening include: annual physical breast examination and annual or biennial mammography for women ages 40-49; annual physical breast examination and annual mammography for women ages 50 and over. The Rhode Island Department of Health's statewide breast cancer screening program is designed to improve compliance with these recommendations. Less than half of Rhode Island women ages 40 and over are receiving annual screening mammograms, but the proportion appears to be increasing (Table 1).

Nearly 60 per cent of Rhode Island women report having

received a recommendation from a medical provider for a screening mammogram, and this proportion appears to be increasing, as well. Recommendations from providers are strongly associated with receipt of screening mammograms.

Sources of data outside the Rhode Island Department of Health:

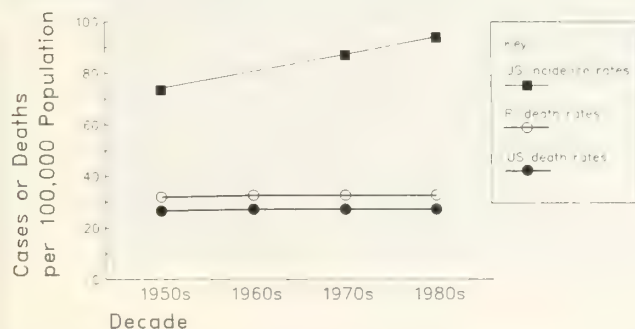
- National Cancer Institute: 1987 Annual Cancer Statistics Review. NCI, NIH Pub No 88-2789, Bethesda, MD, 1988.
- Heston JF, Kelly JAB, Meigs JW, Flannery JT: Forty-five Years of Cancer Incidence in Connecticut: 1935-1979. US Gov Pr Off, Washington, 1986.
- US Environmental Protection Agency and National Cancer Institute: Cancer Mortality Rates and Trends, 1950-1979. US Gov Pr Off, Washington, 1983.

Table 1. Percentage of women 40 years of age and over who have ever had a medical provider recommend a screening mammogram to them, and who have had a screening mammogram in the past year, by provider's recommendation — Rhode Island, 1987 and 1989

Activity	Year	
	1987	1989
Provider ever recommended scr mamm	44%	57%
Had screening mammogram in past year:		
All women	31%	40%
Provider ever recommended scr mamm	60%	58%
Provider never recommended scr mammogram	8%	16%

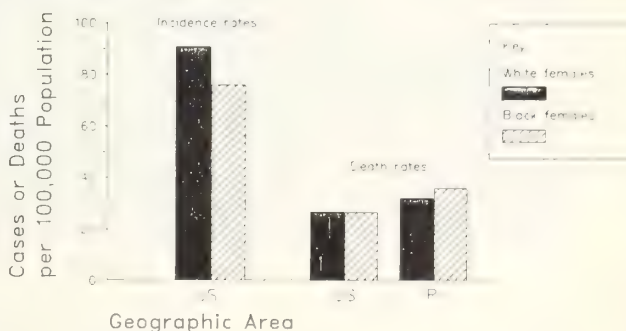
Source: RI Dept of Health statewide surveys of women ages 40 and over, 1987 and 1989.

Figure 1. Breast cancer incidence rates for the US and breast cancer death rates for RI and the US, white females, 1950-1987.



Note: Rates are average annual age-standardized.
Note: Death rates for 1980s cover 1980-85 for US, 1980-87 for RI.
Sources: Death rates: EPA/NCI, 1983; and RIDOH; Incidence rates: NCI, 1988

Figure 2. Breast cancer incidence rates for the US and breast cancer death rates for RI and the US, by race, 1975-1985.



Note: Rates are average annual age-standardized
Sources: NCI, 1988, and RIDOH.

Submitted by the Rhode Island Cancer Registry, John P. Fulton, PhD, Administrator. **Health By Numbers** is edited by Jay S. Buechner, PhD, and William J. Waters, Jr, PhD.

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Monthly Vital Statistics Report

Provisional Occurrence Data From the Division of Vital Records

H. Denman Scott, MD, MPH
Director of Health

Roberta A. Chevoya
State Registrar

Vital Events	Reporting Period	12 Months Ending with June 1989	
	June 1989 Number	Number	Rates
Live Births	1,338	14,869	15.0*
Deaths	755	9,767	9.8*
Infant deaths	(13)	(130)	8.7†
Neonatal deaths	(12)	(98)	6.6†
Marriages	923	8,335	8.4*
Divorces	323	3,863	3.9*
Induced Terminations	635	7,779	523.2†
Spontaneous Fetal Deaths	94	1,113	74.9†
Under 20 weeks' gesta- tion	(85)	(976)	65.6†
20 + weeks' gestation	(9)	(116)	7.8†

*Rates per 1,000 estimated population.

†Rates per 1,000 live births.

Underlying Cause of Death Category	Reporting Period	12 Months Ending with March 1989		YPLL (c)
	March 1989 Number (a)	Number (a)	Rates (b)	
Diseases of the Heart	349	3,606	363.1	5,015.5
Malignant Neoplasms	207	2,441	245.8	7,924.5
Cerebrovascular Diseases	53	620	62.4	950
Injuries(Accident, Suicide, Homicide)	34	439	44.2	9,825.5
Chronic Obstructive Pulmonary Dis- ease (COPD)	27	326	32.8	499

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population.

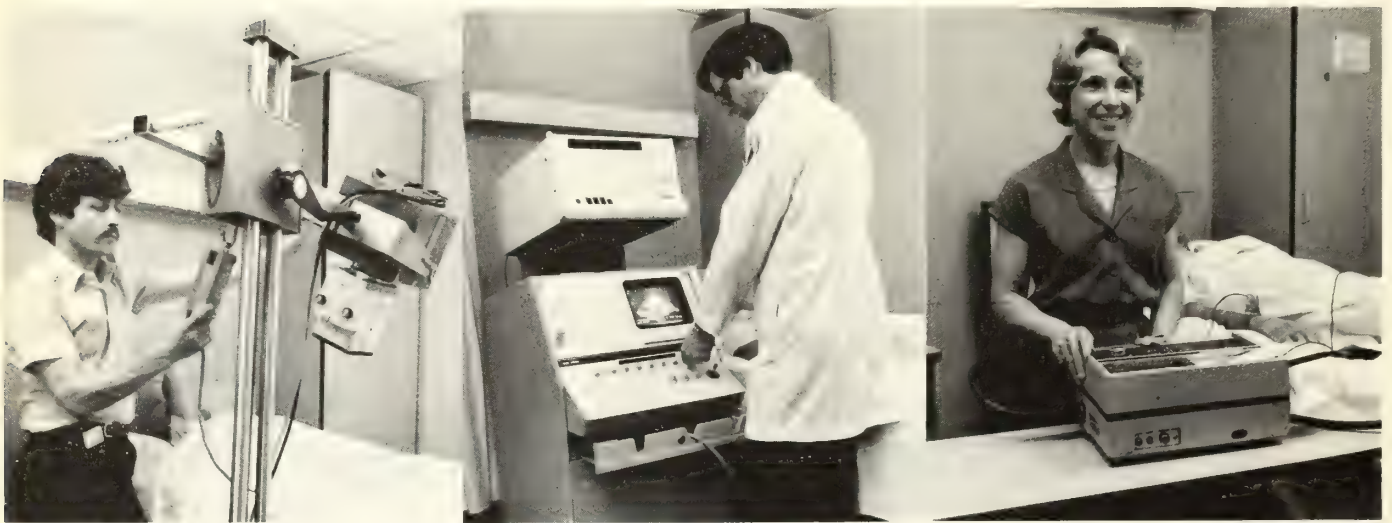
(c) Years of Potential Life Lost (YPLL)

NOTE: Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

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THE RHODE ISLAND MEDICAL JOURNAL

The Official Organ of the Rhode Island Medical Society
Issued Monthly under the direction of the Publication Committee

VOLUME I
NUMBER 1

PROVIDENCE, R. I., JANUARY, 1917

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THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

Fifty Years Ago (October, 1939)

Articles on the use of metrazol therapy for the treatment of schizophrenia, involutional melancholia and other mental disorders, and its hazards, dominate this issue of the *Rhode Island Medical Journal*. The first contribution, by H.E. Kiene, H. Miller, and R.J. Streitwieser, is entitled, "Metrazol Therapy at the Charles V. Chapin Hospital." The authors note that Metrazol treatment of mental disease had begun in Budapest, in 1935. The treatment is described specifically as follows: "Metrazol is administered rapidly intravenously in doses ranging from 3 to 10 cc. The result of the injection, if satisfactory, is an immediate generalized convulsion which lasts about 60 seconds and is associated with extreme cyanosis. Because of the severity of the muscular contractions, fractures and dislocations may occur during the convulsion. It is the belief of the Psychiatric Staff of the Charles V. Chapin Hospital that if there is going to be an improvement, it will be seen after the fourth or fifth injection."

The authors employ this treatment in 59 patients but state that, "The results of the treatment are difficult to evaluate." Nonetheless, they record definite improvement in at least 13 of these 59 individuals. However, when the criterion of disposition [whether the patient is returned home or hospitalized further] is used, the following is noted: "62.8% are at home and 37.2% have been further hospitalized."

Finally, the authors state that "22 cases have been investigated with reference to the possibility of spine injuries. Of this group, six cases have shown pathological changes, chiefly in the mid-dorsal region."

A second paper by C. Rupp summarizes the results of Metrazol therapy at the Rhode Island

State Hospital for Mental Diseases, in Howard. The author concludes: "(1) 18 of 35 schizophrenic patients and 12 of 13 patients with affective psychosis benefited as a result of Metrazol therapy. (2) In the schizophrenic group, the best results were obtained in cases with symptoms of less than 18 months in duration and in the catatonic and paranoid types. (3) No patient requiring tube feeding prior to the onset of treatment failed to begin to eat spontaneously and most patients gained weight. (4) Patients failing to show some improvement by the end of the fifth treatment did not show improvement later, regardless of the number of treatments administered. (5) The only severe complication encountered was the occurrence of compression fractures of the dorsal vertebrae in 13 of 36 cases (36.1%)."

The lead editorial in this month's issue of the *Journal* asks the following question: "The present problem is this: How can the American medical profession continue to carry the steadily increasing load of free service? Economists fail to understand or appreciate the unselfish conduct of medicine in the past and in the present. If there is any answer to this present problem it must be found by organized medicine itself."

The second editorial, entitled "The Hospital Service Plan," describes in some detail the features of The Rhode Island Hospital Service Corporation, known as the Blue Cross, which is now in operation.

The Committee on Necrology reports with deep regret the passing of 18 members during the preceding year.

The 1939 membership of the Rhode Island Medical Society is published in the *Journal*. Of the 495 listed active members, the following 26 physicians are still on the roster of the Society in 1989:

Francis E. Allin
Armand A. Bertini
Francis L. Burns
Louis C. Cerrito
Francis H. Chafee
Morgan Cutts
Stanley D. Davies
Richard H. Dowling
Jesse P. Eddy III
Banice Feinberg
Jay N. Fishbein
A. Henry Fox
Francis E. Hanley

Frank J. Honan
Royal C. Hudson, Jr.
Harry M. Kechijian
Herman B. Marks
Joseph P. Nourie
Rudolph W. Pearson
Marden G. Platt
Mark Rittner
Francis B. Sargent
Ezra A. Sharp
Clara L. Smith
Bernard O. Wise
George L. Young

• • •

lowing: "Due to the construction of Route 95 through Park Street the Library building has been heavily saturated with dust during the spring and summer months and in 1965 we anticipate that the interior of the building will require complete cleaning, and some paint work. The window exterior frames also need painting."

• • •

Twenty Five Years Ago (October, 1964)

Bruce D. Forsyth, DDS, reports on the prevalence of dental caries in permanent and primary teeth eleven years following fluoridation. Fluoridation of the municipal water supply of the greater metropolitan area of Providence had been initiated on August 13, 1952. "In order to justify the expense and later to demonstrate the health benefits of this proved public health procedure, it was determined that an accurate scientific base line data should be collected at the earliest convenience. Between Nov 10, 1952 and Feb 5, 1953, a DMF Dental Caries Survey (i.e., number of decayed, missing, and filled teeth) was conducted by the Rhode Island State Department of Health. It involved a significant sample (8,853 children) of the 35,142 children in the Providence school systems both parochial and public."

A second, post-fluoridation, dental survey was conducted in Providence beginning in Nov 1963 and continuing through April 1964, and 10,630 Providence school children were examined.

The author concludes: "The results after eleven years of fluoridation of the Providence public water supply system are as follows: (1) A striking reduction in the prevalence of dental caries in the permanent teeth of the children in this age group (4 - 17) was effected. It was reduced on the average by about 55 per cent. (2) There was a marked reduction in the prevalence of dental caries in the deciduous teeth. At approximately the peak of prevalence, namely 7 years of age, the rate for the deciduous teeth was reduced by about 48 per cent."

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Specifications: Manuscripts must be original typed copy (not all capitals) on 8½ × 11 inch firm typewritten paper, double-spaced throughout (including title page, text, acknowledgments, and references) with margins of at least one inch and using but one side of each page. Tables, charts, and legends should be submitted separately from the text, and referred to by number (ie, Fig. 1) within the text. Subheadings must be inserted at reasonable intervals to break the typographic monotony of the text. Pages must be numbered consecutively. Italics and boldface print are never used except as subheadings.

Abbreviations: The *Journal* attempts to avoid the use of jargon and abbreviations. All abbreviations, especially of laboratory and diagnostic procedures, must be identified in the text.

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Special arrangements must be made with the editors for excessive numbers of illustrations. Color plates are not acceptable.

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Correspondence: All correspondence relating to publication should be addressed to: Managing Editor, *Rhode Island Medical Journal*, 106 Francis Street, Providence, RI 02903.



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Warnings: **Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including VASOTEC. In such cases, VASOTEC should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL), should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Heart failure patients given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed, caution should be observed when initiating therapy (See DOSAGE AND ADMINISTRATION). Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in heart failure patients), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS). In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: **General:** **Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: Elevated serum potassium (> 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC (See Drug Interactions).

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Hypotension: **Patients on Diuretic Therapy:** Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methylglucosides, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium: A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. Although a causal relationship has not been established, it is recommended that caution be exercised when lithium is used concomitantly with VASOTEC and serum lithium levels should be monitored frequently.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters.

There are no adequate and well-controlled studies of enalapril in pregnant women. However, data are available that show enalapril crosses the human placenta. Because the risk of fetal toxicity with the use of ACE inhibitors has not been clearly defined, VASOTEC® (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome: Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypertension, or the underlying prematurity.

Nursing Mothers: Milk in lactating rats contains radioactivity following administration of ¹⁴C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2987 patients.

HYPERTENSION: The most frequent clinical adverse experiences in controlled trials were headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

HEART FAILURE: The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (8%), headache (8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

Cardiovascular: Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (See WARNINGS, Hypotension), cardiac arrest, pulmonary embolism and infarction, rhythm disturbances: atrial fibrillation, palpitation.

Digestive: Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis.

Nervous/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Urogenital: Renal failure, oliguria, renal dysfunction (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Respiratory: Bronchospasm, rhinorrhea, asthma, upper respiratory infection.

Skin: Herpes zoster, pruritus, alopecia, flushing, photosensitivity.

Other: Vasculitis, muscle cramps, hyperhidrosis, impotence, blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include fever, myalgia, and arthralgia, an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately (See WARNINGS).

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure (See WARNINGS).

Clinical Laboratory Test Findings

Serum Electrolytes: Hyperkalemia (See PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis (See PRECAUTIONS). In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g% and 1.0 vol %, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

Dosage and Administration: **Hypertension:** In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension (See WARNINGS). If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour (See WARNINGS and PRECAUTIONS, Drug Interactions).

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (See PRECAUTIONS).

Dosage Adjustment in Hypertensive Patients with Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine < 3 mg/dL). For patients with creatinine clearance < 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure: VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once or twice daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour (See WARNINGS and PRECAUTIONS, Drug Interactions). If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses (See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects). Dosage may be adjusted depending upon clinical or hemodynamic response (See WARNINGS).

Dosage Adjustment in Heart Failure Patients with Renal Impairment or Hyponatremia: In heart failure patients with hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine > 1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision (See DOSAGE AND ADMINISTRATION, Heart Failure, WARNINGS, and PRECAUTIONS, Drug Interactions). The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

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Parkinson's Disease Update

(see page 393)



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- 1) The original and one copy must be submitted by January 1, 1990 to Secretary, Caleb Fiske Fund, Rhode Island Medical Society, 106 Francis Street, Providence, Rhode Island 02903.
- 2) All papers must be double-spaced and should not exceed 10,000 words.
- 3) The Trustees reserve the right to award one or more prizes.
- 4) The award recipient(s) must transfer copyright privileges to the Trustees of the Caleb Fiske Fund of the Rhode Island Medical Society. The paper will be considered for publication in the *Rhode Island Medical Journal*, subject to review by the Editorial Board.
- 5) The award recipient(s) will be presented with the prize amount, to be determined by the Board of Trustees of the Caleb Fiske Fund, at the Annual Meeting of the Rhode Island Medical Society to be held in May, 1990.

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Cover: *The cover this month shows two line drawings depicting the characteristic posture of a male patient with Parkinson's disease. The drawing was derived from Gowers' great nineteenth century text on diseases of the central nervous system.*

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EDITORIALS

Parkinson's Disease and the Rhode Island Community

The current prevalence of idiopathic Parkinson's disease is estimated to be about one percent of the population older than 60 years. In the state of Rhode Island, this translates to about 1,400 cases of the disease at any one time, an estimate which accords with the number of cases observed and cared for by the practicing neurologists and internists in the community.

The diligent care of patients with this chronic, progressive disorder demands an understanding of the neurochemical and neuropathologic substrates of parkinsonism. In recent years, much experimental and clinical research has been undertaken to provide us with more rational means of intervention in the disease. The current issue of the *Journal* carries a comprehensive review by Joseph Friedman, MD which summarizes recent advances in clarifying the etiology of this puzzling disorder and discusses, as well, the newer modalities in treatment and perhaps even prevention of the disease.

There are voluntary, private agencies in the Rhode Island community which offer effective support and guidance for the Parkinson's disease patient and his family.

The Rhode Island Parkinson's Support Association, the local chapter of the American Parkinson's Disease Association, was founded about ten years ago. It sponsors educational, support, advocacy and fundraising programs. The Association also helps in recruiting suitable patients for experimental trials conducted by the Parkinson's Disease Center at the Roger Williams General Hospital [(401) 456-2231]. Further information may be obtained by writing to: Rhode Island Parkinson Support Association, PO Box 6642, Providence, RI 02904.

The Parkinson's Disease Referral and Information Center, based at Memorial Hospital in Pawtucket, is also sponsored by the American Parkinson's Disease Association. The Center distributes educational material and periodic newsletters, sponsors annual symposia for the health professions, offers an extensive counselling program on problems of daily living, acts as a referral center for access to practicing physicians

with an interest in Parkinson's disease and to adult day care facilities, medication and exercise programs and transportation services. The Center also sponsors support groups throughout the community including a Young Parkinson Support Group which meets monthly at Kent County Memorial Hospital [(401) 737-7000] and a Family Support Group which meets at Memorial Hospital. Further information may be obtained by calling Kathryn A. Cullen, Coordinator, Parkinson's Disease Referral and Information Center, Memorial Hospital of RI, Pawtucket, RI 02860 [(401) 722-6000, Extension 2802.]

Stanley M. Aronson, MD

The Rhode Island Task Force on Teenage Suicide Prevention

The paper by Spirito and colleagues, "Surveillance of Adolescent Suicide Attempters in the Rhode Island Hospital Pediatric Emergency Room," confirms again the gravity of adolescent suicide in our society. The statistics are shocking: Teenage suicide in our country is not only the number two killer of young adults aged 15 to 24 years, but some ten per cent of all young Americans undertake unsuccessful suicide attempts.

Nationally, from 1960 to 1989, the suicide rate for young adults has escalated 260 per cent, during which time 19 of every 100,000 youths took their own lives annually. Specialists in suicide prevention, unfortunately, are pessimistic about any early diminution in this appalling rate.

We in Rhode Island are in the forefront of those who have contended with this truly tragic situation. Earlier this decade legislation was passed making possible the funding for the significant study which appears elsewhere in this issue of the *Rhode Island Medical Journal*. It is my hope that these investigative findings will be the

beginning of yet more intensive community efforts by the Rhode Island Task Force on Teenage Suicide Prevention, established in 1985. The Task Force seeks to raise public awareness regarding the seriousness of the issue and to then formulate rational and constructive public policies based on data of the kind generated by Spirito and his colleagues.

As chairman of the Rhode Island Teenage Suicide Prevention Task Force, I was pleased to work with the Rhode Island Samaritans in obtaining a grant from the National Council of State Legislatures for the establishment of a suicide awareness program in four high schools in Rhode Island. This pilot program was so successful that in 1986 legislation was enacted which required adolescent suicide awareness programs to become a required part of the health education curriculum in all Rhode Island public high schools. Moreover, we obtained funding to enable the Samaritans, Rhode Island's leading suicide prevention agency, to hold teacher training workshops and to distribute suicide prevention materials throughout the state.

I am particularly pleased that Dr Spirito's data suggests that Rhode Island's high school suicide awareness programs may lead "... to knowledge and attitude change." It is obvious that a true measure of the success of these efforts must await follow-up studies, but these early findings are both positive and encouraging.

We must all face the fact that our young people are destroying themselves at an alarming rate and that our society must find ways of stopping this disastrous loss of precious life. Suicide is preventable. We know now that education and early intervention are key elements in helping youth find the support they require to address their problems. We must provide this support so that our teenagers will know that they are not alone and that there are ways to break this terrible pattern of self-destruction.

The Honorable Richard A. Licht

On Medical Abbreviations

In bygone decades medical abbreviations were limited essentially to such common shortenings as the universally understood phrases which begin so many medical histories, "*The patient was a*

wd, wn, wm who..." These repetitious abbreviations represented both a time-saving mechanism as well as an internal jargon serving to separate physicians from non-physicians. They were harmless amusements for senior medical students and practical blessings for harried and overworked interns. The number of complex pharmacological agents in past years had been limited and when employed were rarely expressed in terms of molecular structure or as abbreviations.

Clearly, there is utility in employing abbreviations within scientific texts. MPTP is easier, quicker to say or read than 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine. Current editorial practice with most medical or biological journals dictates that such abbreviation be inserted parenthetically immediately following the first usage of the full term. Subsequently, the abbreviation is used in the place of the longer word or phrase. This system works well when the undistracted reader begins at the beginning of the article and reads each paragraph in proper sequence. The realities, however, are otherwise.

Most busy physicians do not read a journal article as though they were preparing for an examination on its scientific content. Rather, they randomly scan articles, frequently proceeding backwards, and often reading the summary before the introductory text. And inevitably they will encounter lines such as: "... and the newer agents, particularly PQWW, are found to be more effective, especially in the LGB syndrome." Unless they are blessed with uncommon imagination the educational value of the article vanishes until the PQWW's and LGB's can be deciphered. This then entails a frantic search through the earlier paragraphs of the article seeking the first usage of the abbreviation [and hence with it, the full term.] These hasty excursions through the article are time-consuming, unproductive and sometimes maddening.

In recognition of the realities that most of us do not include MPTP, ITP, LGB, and PQWW in our daily conversations, the editors of the *Rhode Island Medical Journal* shall henceforth adopt a new policy clustering all identified abbreviations within a clearly visible box at the lower right-hand corner of the first page of those articles which require obscure abbreviations within their context. Brevity, said Shakespeare, is the soul of wit, but he was never required to read weighty medical journals between patient visits.

Stanley M. Aronson, MD

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1. For the treatment of patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis. If hypokalemia is the result of diuretic therapy, consideration should be given to the use of a lower dose of diuretic, which may be sufficient without leading to hypokalemia.

2. For the prevention of hypokalemia in patients who would be at particular risk if hypokalemia were to develop, e.g., digitalized patients or patients with significant cardiac arrhythmias.

The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern and when low doses of the diuretic are used. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases, and if dose adjustment of the diuretic is ineffective or unwarranted, supplementation with potassium salts may be indicated.

CONTRAINDICATIONS Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene, amiloride) (see **OVERDOSAGE**).

Controlled release formulations of potassium chloride have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be given as a liquid preparation or as an aqueous (water) suspension of K-DUR (see **PRECAUTIONS, Information for Patients**, and **DOSE AND ADMINISTRATION** sections).

All solid dosage forms of potassium chloride are contraindicated in any patient in whom there is structural, pathological (e.g., diabetic gastroparesis) or pharmacologic (use of anticholinergic agents or other agents with anticholinergic properties at sufficient doses to exert anticholinergic effects) cause for arrest or delay in tablet passage through the gastrointestinal tract.

WARNINGS Hyperkalemia (see **OVERDOSAGE**)—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone, triamterene or amiloride) since the simultaneous administration of these agents can produce severe hyperkalemia.

Interaction with Angiotensin Converting Enzyme Inhibitors—Angiotensin converting enzyme (ACE) inhibitors (e.g., captopril, enalapril) will produce some potassium retention by inhibiting aldosterone production. Potassium supplements should be given to patients receiving ACE inhibitors only with close monitoring.

Gastrointestinal Lesions—Solid oral dosage forms of potassium chloride can produce ulcerative and/or stenotic lesions of the gastrointestinal tract. Based on spontaneous adverse reaction reports, enteric coated preparations of potassium chloride are associated with an increased frequency of small bowel lesions (40-50 per 100,000 patient years) compared to sustained release wax matrix formulations (less than one per 100,000 patient years). Because of the lack of extensive marketing experience with microencapsulated products, a comparison between such products and wax matrix or enteric coated products is not available. K-DUR is a tablet formulated to provide a controlled rate of release of microencapsulated potassium chloride and thus to minimize the possibility of a high local concentration of potassium near the gastrointestinal wall.

Prospective trials have been conducted in normal human volunteers in which the upper gastrointestinal tract was evaluated by endoscopic inspection before and after one week of solid oral potassium chloride therapy. The ability of this model to predict events occurring in usual clinical practice is unknown. Trials which approximated usual clinical practice did not reveal any clear differences between the wax matrix and microencapsulated dosage forms. In contrast, there was a higher incidence of gastric and duodenal lesions in subjects receiving a high dose of a wax matrix controlled release formulation under conditions which did not resemble usual or recommended clinical practice (i.e., 96 mEq per day in divided doses of potassium chloride administered to fasted patients, in the presence of an anticholinergic drug to delay gastric emptying). The upper gastrointestinal lesions observed by endoscopy were asymptomatic and were not accompanied by evidence of bleeding (Hemoccult testing). The relevance of these findings to the usual conditions (i.e., non-fasting, no anticholinergic agent, smaller doses) under which controlled release potassium chloride products are used is uncertain; epidemiologic studies have not identified an elevated risk, compared to microencapsulated products, for upper gastrointestinal lesions in patients receiving wax matrix formulations. K-DUR should be discontinued immediately and the possibility of ulceration, obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS General: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: When blood is drawn for analysis of plasma potassium it is important to recognize that artifactual elevations can occur after improper venipuncture technique or as a result of in-vitro hemolysis of the sample.

Drug Interactions: Potassium-sparing diuretics, angiotensin converting enzyme inhibitors (see **WARNINGS**).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity, mutagenicity and fertility studies in animals have not been performed. Potassium is a normal dietary constituent.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is unlikely that potassium supplementation that does not lead to hyperkalemia would have an adverse effect on the fetus or would affect reproductive capacity.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS, and OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS and WARNINGS**).

The most common adverse reactions to oral potassium salts are nausea, vomiting, flatulence, abdominal pain/discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals or reducing the amount taken at one time.

OVERDOSAGE The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS and WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration (6.5-8.0 mEq/L) and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest (9-12 mEq/L).

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of any agents with potassium-sparing properties
2. Intravenous administration of 300 to 500 mL/hr of 10% dextrose solution containing 10-20 units of crystalline insulin per 1,000 mL.

3. Correction of acidosis, if present, with intravenous sodium bicarbonate

4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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Parkinson's Disease Update

Joseph H. Friedman, MD

The major breakthroughs in Parkinson's disease (PD) that I expect to occur by the end of this century are: An understanding of the cause of PD and the development of methods to prevent it; development of affordable techniques to diagnose PD before it becomes symptomatic and the identification of medications to slow or halt its progression; development of more effective medications and brain implantation methods to better treat those with active disease.

Research on Parkinson's disease (PD) has mushroomed dramatically in recent years. An initial flurry of activity occurred around 1960 with the discovery of the dopamine deficit¹ followed in 1969 by the equally impressive development of L-DOPA as an effective therapy for symptoms of the illness.² Progress then slowed, until the discovery in 1982 that 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP), a narcotic derivative drug sold on the streets of California³ caused severe parkinsonism in humans. It was soon discovered that it also caused parkinsonism in primates, thus providing the first primate model of PD.⁴ Current research focuses on etiology, pathophysiology and treatment.

Etiology Considerations

In terms of etiology little is known. PD is not thought to be due to an infectious agent or to be hereditary.⁵ Although there clearly existed a form of parkinsonism associated with encephalitis lethargica (Von Economo's encephalitis), the cohort hypothesis that all PD was due to this infection and that all cases would disappear as the popu-

lation exposed to the virus (the cohort) aged, proved to be incorrect. Post-infectious parkinsonism has a different pathology and course than idiopathic PD and while the former is disappearing, the latter is not. Isolated cases of the post-infectious form are still reported⁶ but the viral agent has not been identified in all cases. The vast bulk of the infectious cases occurred during the time of the great influenza epidemic of the early nineteen twenties. There is only circumstantial evidence to support a common viral etiology for both.⁷

The hereditary aspects are not completely clear. A study of identical twins, of whom one has PD, has shown no increased incidence of PD in the other twin.⁵ On the other hand, specialists in PD have been impressed with families that seem to have a markedly increased incidence of PD, raising the issue of hereditary forms of the illness.

ABBREVIATIONS USED:

DATATOP: Deprenyl Tocopherol Antioxidative Therapy of Parkinsonism

L-DOPA: 3,4-dihydroxy-L-phenylalanine

MPTP: 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine

PD: Parkinson's disease

PET: positron emission tomography

PHNO: 4-propyl-9-hydroxynaphthoxazine

SND-19: Pramipexole.

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Since it is so common, occurring in one percent of the American Caucasian population over 60, it has been impossible to determine whether these familial clusters are simply random. At the Parkinson's Disease Center at the Roger Williams General Hospital I have recently seen a 28-year-old woman with PD whose sister died with advanced, pathologically confirmed PD. Another family has three siblings and a niece all with PD. Other familial clusters, although with later disease onset, are not uncommon in this area.

... a narcotic derivative drug sold on the streets of California caused severe parkinsonism in humans.

Most investigators in the field believe that environmental agents are important in causing PD but evidence is circumstantial and not yet compelling.⁸ The concept of an environmental cause is based as much on the lack of an identified infectious or hereditary etiology as it is on solid clues. The suggestive evidence derives from observations that naturally occurring toxins do cause parkinsonian syndromes. Star thistle, a weed, causes parkinsonism in horses.⁹ Manganese dust, found in factories and mines, carbon monoxide and cyanide all cause irreversible PD in humans. MPTP, a synthetic compound related structurally to many naturally occurring compounds, not only causes parkinsonism in humans but selectively affects brain nuclei which have been shown to degenerate in PD. Perhaps the most impressive circumstantial evidence was the discovery that a toxic compound in a tuber that was a dietary staple on Guam before World War II causes a clinical syndrome and pathological changes in primates identical to the naturally occurring degenerative disease called the Guamanian amyotrophic lateral sclerosis-Parkinson's disease-dementia complex.¹⁰ This had been the leading cause of death on the island until the population adopted western customs and reduced its consumption of the tuber. Thus, another slowly progressive disorder involving some of the same brain structures as in PD appears to be due to an environmental agent.

It is most likely that PD is caused by one or more environmental substances that are naturally occurring and for which a hereditary predisposition may play a role.¹¹ A recent published study revealed elevated copper concentrations in cerebrospinal fluid of untreated PD patients,¹² suggesting the possibility of a metabolic de-

range, either causal or secondary to the PD, but attempts to confirm this have found no differences between patients and controls.¹³

One recent hypothesis concerning disease progression suggested that PD might reflect a single or perhaps a few isolated toxic exposures which damaged some cells in the substantia nigra but not sufficient numbers to cause clinical disease.⁸ Normal aging, which causes a further drop out in the substantia nigra neurons would, in conjunction with the prior toxic damage, then cause the final decline to PD. Work by McGeer et al¹⁴ has shown that PD patients actually have a much increased rate of neuronal loss compared to controls, suggesting that PD is an active process throughout its clinical course.

Pathological Considerations

The pathophysiology of parkinsonian signs has been somewhat better understood with the aid of MPTP.^{3,4,8} This narcotic derivative causes neuronal death in the pars compacta of the substantia nigra in primates and other animals. This is one of the locations affected in PD.⁴ Over twenty IV drug abusers developed irreversible parkinsonism as a result of getting high on MPTP. In the one human studied pathologically after the use of MPTP, as well as in the primate models, it became apparent that virtually all of the clinical features of human PD could be ascribable to the loss of cells in the pars compacta. The dysfunction caused by alterations in the other brain regions (locus ceruleus, dorsal motor nucleus of the vagus nerve) in idiopathic PD therefore largely remains unexplained. One theoretically important aspect of this discovery is the implication that brain implantations may be feasible, since the functions of only one brain region need replacement, rather than many discrete regions. An additional observation that had been suspected prior to the MPTP discovery was that clinical signs and symptoms of parkinsonism did not emerge until 80 per cent⁸ or more of the cells in the pars compacta were lost, implying a four-fold redundancy in the system and more importantly, implying that neuronal circuitry was less important in the neuronal system than neurohormonal balance. That is, the chemical balance, or level of dopamine was crucial, not the synaptic connections. Thus, this aspect of brain function is not simply a computer-like model in which the connections are critical. Failure in this part of the brain might therefore be amenable to chemical implants or tissue implants even though the neuronal circuits will never regenerate.

Therapeutic Considerations

The drug treatment of PD has not changed dramatically in recent years but may soon. Possibly the most important development has been the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) study, a \$10,000,000 NIH-sponsored multicenter prospective study to test whether deprenyl (Selegiline) and/or tocopherol (Vitamin E), both antioxidants, can slow the progression of mild, untreated PD. A pilot study recently reported that deprenyl does indeed prolong the time interval before an otherwise untreated PD will require symptomatic therapy¹⁵ and hence it appears to slow disease progression. This represents the first attempt to treat the disease itself, ie, the degeneration and the death of neurons, rather than just the symptoms (rigidity, tremor, bradykinesia, etc). DATATOP is the largest study ever undertaken on PD, involving 800 untreated patients. The results of this study are not yet available since it is still in progress. Hopefully it will confirm the results of the pilot project.

Most investigators believe that environmental agents are important in causing Parkinson's disease.

The rationale for the deprenyl study was both theoretical and clinical. The theoretical background lies partly in the belief that free radicals, resulting from oxidative chemical reactions, are harmful to neurons. Similar theories have been raised for cancer and for aging.¹⁶⁻¹⁷ Since dopamine synthesis in the neuron creates free radicals, slowing this reaction might preserve the neurons. Deprenyl acts by blocking the enzyme monoamine oxidase B, which metabolizes dopamine. Thus deprenyl prolongs the action of dopamine, reducing the synthesis of dopamine and hence the generation of free radicals. Tocopherol is a free radical scavenger and acts in a non-specific manner to reduce free radical concentrations. Another theoretical rationale for deprenyl is its ability to render MPTP non-toxic, suggesting the remote possibility that if deprenyl can block the toxicity of one PD-inducing compound, it might be inhibitory for other neurotoxins as well. Finally, a retrospective European study¹⁸ observed that deprenyl prolonged functional ability and delayed death in treated PD patients. As DATATOP was launched well before the results were available on the smaller deprenyl study, it is comforting to learn that an

independent trial has borne out the hypotheses under evaluation.

The benefit of finding a way to slow down PD progression is not limited to providing the appropriate medication to any individual PD patient. Since signs and symptoms of PD do not emerge until several years after the actual loss of neurons begins to occur (ie, when the last 20 per cent of the nigral cells start to deteriorate) one might, theoretically, forestall the actual symptoms of the illness if treatment were started in the pre-clinical stage. This possibility may soon be tested. PET (positron emission tomography) scans are currently able to create CT scan-like images of the brain, providing information on regional neural metabolism. With suitable radioactive isotopes, dopamine and dopamine receptors can be labelled to provide in vivo evidence of dopamine content throughout the brain. Should PET scans or other similar studies ever become inexpensive, safe and widely available, the at-risk population could be screened to identify and then treat those patients before symptoms of PD occur, thus aborting the clinical appearance of the disease.

A significant amount of work has gone into understanding why some patients suffer from clinical fluctuations in response to L-DOPA. In a large study evaluating the response to L-DOPA in previously untreated PD patients, in treated but stable patients, and in those patients with clinical fluctuations and those with "on/off" (seemingly random, sudden oscillations) several interesting findings emerged.^{19,20} Previously untreated patients responded to L-DOPA for six hours or more despite the fact that the serum half-life of the drug is only 90 minutes. Treated patients without fluctuations had a stable response for a shorter period of time. Clinical fluctuators had a short response and "on/off" patients the shortest. The fluctuators and "on/off" patients all had dyskinesias when "on" and severe parkinsonism when "off," without an intermediate state. One can infer that two things occur over time as PD patients are treated with L-DOPA. The first is that storage capacity for the L-DOPA decreases. Thus, when the patient has mild PD and 10-15 per cent of the nigral neurons are intact, L-DOPA can be stored and dopamine synthesized over several hours, even after the plasma level of drug is nil. As the disease worsens and nigral neurons die, less and less L-DOPA can be stored. When the disease is advanced and only 2-5 per cent of nigral neurons remain there is virtually no storage capacity and the brain is de-

pendent upon a constant plasma level to supply L-DOPA. The threshold at which patients responded to L-DOPA was the same in all groups of patients so that even advanced PD patients never developed a resistance to the drug. The second implication of these studies is that, over time, the therapeutic window for plasma L-DOPA levels narrows. It eventually becomes impossible for some patients to achieve a plasma drug level resulting in a good response without dyskinesias.

The search for better treatment of PD symptoms continues. Pergolide, a direct dopamine agonist similar to bromocriptine has recently reached the pharmacies. Its indications for use will be similar to those of bromocriptine: predominantly as an adjunct to L-DOPA. Its major importance is that many patients who were intolerant of bromocriptine because of nausea or dizziness (usually lightheadedness) may tolerate pergolide at doses high enough to provide symptomatic relief. Its efficacy is similar to that of bromocriptine.

... deprenyl prolonged functional ability and delayed death in treated Parkinson's disease patients.

Deprenyl (Selegiline), a monoamine oxidase B inhibitor, has been approved for marketing by the FDA. It is a helpful adjunctive medication to sinemet for patients with a clinically fluctuating response to L-DOPA. The main interest about it concerns its possible ability to slow progression of the disease. PHNO, (4-propyl-9-hydroxynaphthoxazine) a direct dopamine agonist that can be absorbed through the skin (and hence providing a constant level of drug in the blood) currently is under study.²¹ SND² 919 is a drug with a novel action. In animal models of parkinsonism it appears to act as a direct dopamine agonist while in animal models of schizophrenia, it behaves as a dopamine receptor blocking agent. This drug is effective in the MPTP primate model of PD and will receive its first American human trials in Providence.

Paradoxically, a major breakthrough in the drug treatment of schizophrenia also represents an advance in the treatment of PD. This is paradoxical because schizophrenia is often considered a dopamine excess state whereas PD is a dopamine deficiency state. How important an advance this is will be determined over the next few years. Clozapine, an atypical neuroleptic that causes virtually no extrapyramidal side effects (such as parkinsonism, akathisia, acute dystonia,

or tardive dyskinesia) has been demonstrated to be a more potent antipsychotic agent than any known medication.²² Although it shares the dopamine receptor blocking action of the other antipsychotics, it does so to a significantly lesser degree and has many other pharmacological properties. It is apparently useful in PD in two ways. It is extremely helpful in managing psychoses in PD patients.²³ There are only two currently available approaches to managing this problem: either reduce PD medications, since these drugs can exacerbate or cause organic mental changes, or add an antipsychotic agent. Agents other than clozapine cause parkinsonism in normal patients and exacerbate it in those with PD. Similarly, reducing PD medications will worsen the parkinsonism. Clozapine does neither. It may become, therefore, the drug of choice in this situation. Clozapine also lessens tremors, both in PD and in essential tremor. My own experience in PD certainly bears this out but we do not yet know how long the benefit will be sustained. We have so far treated six patients with very small doses of clozapine after their PD tremor had failed to respond to standard PD medications, and have had moderate to marked success.²⁴

Tissue Transplantation as Therapy

Yet another area of active PD research is in brain implantation. There have been two approaches: one uses autologous adrenal medullary tissue; the other uses fetal substantia nigra. In animal models this approach works better; however the brain is not a privileged immunologic site and transplants are often rejected. Thus, the HLA matching between host and donor assumes great importance. This potential incompatibility makes fetal implantation problematic. An alternative approach has been to use the subject's own adrenal medullary tissue. The method uses cells which secrete epinephrine (adrenaline) which is derived from dopamine. These transplanted cells alter and evolve into neuronal-type cells. Adrenal implants into animal brains were mildly successful but the first few human trials were unsuccessful.²⁵ In 1987 a Mexican team announced the successful use of autologous adrenal implants to treat PD.²⁶ The results seemed impressive and several institutions around the world sought to reproduce the work, while several prestigious centers chose not to perform the operation pending further evaluation.

More than 200 adrenal transplant operations have been performed in this country. Results have been generally disappointing. Although some

patients have shown significant benefits, the procedure carries a considerable morbidity and mortality.²⁷ Some investigators believe that any improvement is related only to a persisting blood brain barrier disruption while others think that it has to do with trophic factors released by the damaged brain.

Virtually all American hospitals have now abandoned the adrenal implant procedure. The use of human fetal tissue derived from abortions still holds some promise. In Mexico, several such procedures were performed using donor tissue from spontaneous miscarriages.²⁸ This required that host subjects live in the hospital waiting for a suitable donor. The host then requires immunosuppression for life to prevent rejection. At least three such operations were performed in the United States and more in England but results are unavailable. A published report on two patients from Sweden described only mild improvement.²⁹

Results (of adrenal tissue brain transplants in Parkinson's disease patients) have been generally disappointing.

Alternate Transplantation Techniques

Since tissues compatibility is essential and since availability of donor tissues is fairly random, other approaches have been investigated. One involves the freezing of donor fetal brain. In this way donor tissue can be banked so that properly matched cells might be used on an elective basis. In another approach, genetic engineering has been used to induce dopamine synthesis in fibroblasts. Theoretically, a patient may donate some skin cells for in vitro genetic alteration and then have them implanted into the subject's own brain.

Experiments with selectively permeable membranes are being conducted at Brown University's Artificial Organs Laboratory. These membranes, encapsulating cells, have pores large enough to allow neurotransmitters to be released but small enough to block passage of cells, thus preventing rejection. Experimentally transplanted cross-species brain grafts survive long-term, without immunosuppression, and can reverse parkinsonism in rodent models. Techniques have been developed to measure and titrate the amount of dopamine secreted by such encapsulated cells. If the transplants survive and function in the MPTP primate model of PD and are shown to be safe, they could then be tried on humans. This procedure would be performed

via stereotactic surgery under local anesthesia, thus eliminating much of the morbidity of the two operations required for the adrenal transplant procedure. No immunosuppression will be required. Unlike human fetal implantation, these implants will be derived from fetal animals.

Comment

The major breakthroughs in PD that I expect to occur by the end of this century are: an understanding of the cause of PD and the development of methods to prevent it; development of affordable techniques to diagnose PD before it becomes symptomatic and the identification of medications to slow or halt its progression; development of more effective medications and brain implantation methods to better treat those with active disease.

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Surveillance of Adolescent Suicide Attempters in the Rhode Island Hospital Pediatric Emergency Department

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Efforts to understand completed suicide increasingly focus on the related problem of attempted suicide.

Adolescent suicide is a serious social problem and is recognized as the second leading cause of death in the teenage years.¹ Retrospective psychological studies indicate that a substantial number of adolescents who complete suicide have made prior suicide attempts.^{2, 3} Moreover follow-up studies show that a significant number of adolescent suicide attempters will also go on to complete suicide.^{4, 5} Thus, efforts to understand completed suicide increasingly focus on the related problem of attempted suicide. The exact magnitude of non-fatal adolescent suicidal behavior is difficult to estimate since relatively few of these attempters receive medical care.⁶ However, in anonymous surveys, approximately ten per cent of adolescents admit to prior suicide attempts.^{6, 7} The

frequent occurrence of suicide attempts in adolescents is of concern not only because of the possibility of completed suicide, but also because of significant physical and psychological comorbidities.

Given the magnitude of the problem of attempted suicide and completed suicide in adolescents, comprehensive surveillance data on attempters is indicated. Indeed, the Violence Epidemiology Branch of the Centers for Disease Control has called for more detailed statistics regarding suicide at both the state and local levels.⁸ Local studies of adolescent suicide attempts can help define the magnitude and nature of this problem in specific areas. The data collected may help facilitate the development of prevention ef-

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forts utilizing both population-based and clinical approaches.⁹ Such studies may also help document changes in suicide patterns and incidence rates across time. The findings of a surveillance system established at the Rhode Island Hospital Pediatric Emergency Department, through the sponsorship of the Lieutenant Governor's Commission on Youth Suicide and the Rhode Island Department of Health, are presented below.

Subjects

The studied population consisted of 195 adolescent suicide attempters seen in Rhode Island Hospital's Pediatric Emergency Department. A retrospective chart review of all 1986 pediatric admissions, approximately 19,000 patients, identified 110 suicide attempters. In addition, a prospective daily chart review of suicide attempters seen in the emergency room in 1988 revealed an additional 85 cases. The record of any patient with a discharge diagnosis of suicide attempt was included. Patients with discharge diagnoses in ICD 9-CM *External Cause of Injury Codes* that might have represented a suicide attempt, eg, arm and wrist lacerations, asphyxia, unintentional hanging, and drug and alcohol overdoses, were reviewed and included in the sample if the injury arose secondary to a suicide attempt but suicide attempt had not been the discharge diagnosis. There was no attempt to distinguish between suicidal "gestures" and suicidal "attempts"¹⁰; any intentional self-injury, lethal or not, was considered a suicide attempt if the adolescent admitted the purpose of the self-injury was for self-harm.

Procedure

Emergency Room Record Review

A trained research assistant reviewed the emergency room records of all adolescents to extract sociodemographic information. Social class was determined by using the Rhode Island Census Tract Data¹¹; subjects were placed into one of four socioeconomic strata: High, medium, low and poverty, based on their street address. The extraction of other information varied according to the extent of the emergency room record. Thus, we were unable to obtain complete information on certain questions such as the number of previous attempts and prior mental health contacts. This accounts for the variation in the number of subjects shown in Tables 1 and 2.

Rating of Attempt Lethality

A subset of the entire sample, consisting of 82 female and 27 male suicide attempters who were admitted as inpatients, were also rated by the

Table 1. Sociodemographic Characteristics of Adolescent Suicide Attempters Seen in the Rhode Island Hospital Pediatric Emergency Department

	Attempters (%)
Sex	
Male	17.4
Female	82.6
	(N = 195)
Age (years)	
10-12	2.6
13	5.6
14	22.6
15	26.7
16	21.0
17	17.9
18	3.6
	(N = 195)
Race	
White	78.2
Nonwhite	21.8
	(N = 193)
Social Class	
High	25.4
Medium	33.7
Low	23.8
Poverty	17.1
	(N = 181)

Risk-Rescue Rating Scale.¹² This scale, completed by trained raters, assesses medical lethality of the suicide attempt. The Risk Scale, consisting of two separate subsections is composed of five items reflecting the danger of the attempt. The items include a rating of the agent used, level of impaired consciousness, toxicity of the attempt, medical reversibility, and treatment required. The Rescue Scale also examines those factors of the attempt which impede rescue. The five items that relate to rescue potential include: location of the attempt, the person who initiates the rescue, the probability of discovery, accessibility to rescue, and delay until discovery.

Results

The first set of analyses involve a series of Chi-square tests to determine if there are differences between the 1986 and 1988 samples. Using a conservative p level (.01) to control for Type I error due to multiple comparisons, only the degree of isolation at the time of the attempt differed by year, ($\chi^2 = 11.5$, $p < .003$). Subjects in 1986 reported that no one was nearby at the time of the attempt (17.2 per cent) more often than subjects in 1988 (4.2 per cent). Since this item was rated by retrospective chart review in 1986 and prospectively in 1988, the different findings may be a function of the method of data extraction rather than a general change in suicidal behavior. Since there were no other differences by

Table 2. Incident Characteristics of Adolescent Suicide Attempts

	Attempters (%)
Period of Incident	
January-April	46.4
May-August	25.3
September-December	28.4
	(N = 194)
Time of Incident	
12-5:59 a.m.	16.5
6-11:59 a.m.	11.4
12-5:59 p.m.	27.8
6-11:59 p.m.	44.3
	(N = 194)
Day of Incident	
Sunday	14.3
Monday	14.3
Tuesday	17.4
Wednesday	15.4
Thursday	9.7
Friday	12.9
Saturday	16.0
	(N = 194)

year, the data were combined into one sample.

Table 1 reflects the sociodemographic characteristics of our sample; specifically, sex, age, race, and social class distribution. Table 2 describes incident characteristics of the suicide attempts. Data on the method, Risk-Rescue rating of the method's lethality, precipitating event, consumption of alcohol, isolation at the time of the attempt, and presence or absence of a suicide note, are presented in Table 3. Prior suicide attempts and mental health contacts, as well as disposition status following the Emergency Room visit are also reported in Table 3.

Discussion

Characteristics of Sample

Descriptive data were collected on adolescent suicide attempters seen in the Rhode Island Hospital Emergency Room during 1986 and 1988. Consistent with other observations^{9, 13, 14} suicide attempters were predominantly female. The mean age of about 15 years was similar to that of other emergency room studies.^{13, 15} There was also a relatively even distribution of attempters by social class. The variation in attempt rate across seasons seen in this population has also been noted in other studies of suicide attempters seen in emergency rooms. An increase during winter months and a slight decrease during spring and summer has been noted.^{9, 13} The suicide attempts in the currently studied group usually occurred in the evening, similar to the pattern documented in other studies.¹³

In our sample, the characteristics of the suicide

attempt are similar to those reported in the majority of other studies of adolescent suicide attempters. The primary means for attempting suicide is by drug overdose.^{9, 14, 15} Our rate of 86.2 per cent is comparable to that of a large emergency room study conducted by Garfinkel and colleagues in Canada, who found 88 per cent of suicide attempts were by drug overdose.¹³ Ratings of the lethality of the attempt on the Risk-Rescue (RR) Scale, revealed a majority of low lethal attempts which are not peculiar to this sample of suicidal adolescent.¹⁶ One study¹³ reported that 78 per cent of their RR ratings were of low lethality, 21 per cent were of moderate lethality, and 1 per cent were of high lethality. Alcohol or drug use at the time of the admission was rather low (9.2 per cent), and this was also found in the study by Garfinkel (11.3 per cent). In addition, the fact that others were nearby, or even in direct contact at the time of suicide attempt, is again very similar to other studies with adolescents.¹³

Previous mental health contacts were surprisingly frequent (55.9 per cent), and once again this seems to be characteristic of other studies.^{13, 17} This may reflect adequate access to mental health services but that such services evidently had not been very effective in preventing further suicide attempts. Thus, we need more information on the interaction of these adolescents with mental health services in the community. How does intervention affect the natural history of a suicidal adolescent? What is the nature of services received and what are determinants of compliance? The large number of the current sample who had prior contact with mental health facilities may indicate the considerable extent of a preexisting mental disorder in this population. A fairly large percentage had previously attempted suicide (38.4 per cent), similar to the 37 per cent found in the Canadian study.¹³

The typical pre-adult suicide attempter in Rhode Island is a 15-year-old white female who attempts suicide using pills at home, in the evening, with family members nearby. Most of these attempts are not of a highly lethal nature.

Suicide Attempters versus Suicide Completers

One useful purpose of collecting suicide surveillance data is to compare the characteristics of suicide attempters to suicide completers. In the years 1975 to 1986, there were 96 Rhode Island adolescents who committed suicide. The characteristics of 70 of these suicides have been discussed in this *Journal*.¹⁸ About 84 per cent of the suicide completions were by males while, in this study, 82.6 per cent of suicide attempts were by

females, a pattern consistent with other national studies.^{13, 14, 17} All suicides in this study were white; a small percentage of attempters seen in the Rhode Island Hospital Emergency Room were non-white. The methods associated with fatal suicide in Rhode Island are identical to those reported nationally² and in Canada,¹⁹ but are quite different from the methods used in attempted

suicide. Approximately 30 per cent of completed adolescent suicides in Rhode Island are due to firearms, and another 28 per cent are the result of hanging.¹⁸ These two methods account for only 2 per cent of the methods used in attempted suicides. Conversely, whereas 86.2 per cent of the suicide attempts are by drug overdose, only 13 per cent of the completed suicides are secondary to overdose. The male completers were more likely to use guns and hanging than the female completers. It is not known whether the differences in lethality between attempters and completers are attributable to host factors or lack of access to more lethal methods. Case-control studies and surveys of the household environment of adolescents for the availability of suicide methods are necessary to devise prevention strategies. For example, such a study may help to answer the question of whether completed suicides are preventable by restricting home access to knives, guns, alcohol, or pills.

At the time of death, alcohol is detected in approximately 36 per cent of the suicide completers,¹⁸ whereas among the suicide attempters, alcohol presence is more limited (9.2 per cent). About 21 per cent of the suicide completers had made a prior suicide attempt; among suicide attempters this rate is somewhat higher (38.4 per cent). In examining events precipitating suicidal behavior, parent/family problems were one of the principal causes of both completed and attempted suicide. Ten (14 per cent) of the adolescents who completed suicide had a school problem as the apparently primary precipitant, slightly higher than that obtained in our current sample (8 per cent).

The essential agreement between other studies and our own has implications for social agencies, physicians, and schools. For example, since most suicide attempts occur secondary to rather common stressors, ie, a boyfriend/girlfriend problem or parent/family conflict, it might be worthwhile for pediatricians and social agencies to educate parents, teachers, and adolescents about the role of these stressful events in triggering an impulsive suicide attempt in an at-risk youngster. Efforts at primary prevention are currently underway in Rhode Island in the form of suicide awareness programs in the high schools. Preliminary findings suggest that such programs may lead to a knowledge and attitude change.¹⁹ Whether it leads to a reduction in the attempt rate remains to be seen.

Continued surveillance of suicide attempts in the emergency rooms in the state will be needed to determine if these various prevention efforts

Table 3. Psychiatric history, characteristics of the attempt, and disposition pattern

	Attempters (%)
Method of Attempt	
Drug overdose	86.2
Firearms	0.0
Hanging	2.0
Other	11.8
	(N = 195)
Risk Scores from Risk-Rescue	
High risk	1
High moderate	7
Moderate	35
Low moderate	44
Low risk	13
	(N = 109)
Rescue Scores from Risk-Rescue	
Least rescuable	0
Low moderate	1
Moderate	26
High moderate	37
Most rescuable	36
	(N = 109)
Precipitating Event to Suicide Attempt	
Parents/Family	40.4
Boyfriend/Girlfriend	25.7
School	8.2
Friend	4.4
Other	21.3
	(N = 183)
Consumption of Alcohol at Time of Attempt	
Yes	9.2
No	90.8
	(N = 174)
Isolation at Time of Attempt:	
Someone present	36.5
Someone nearby	52.2
No one nearby	11.3
	(N = 159)
Prior Mental Health Contacts:	
Yes	55.9
No	44.1
	(N = 161)
Number of Previous Suicide Attempts:	
None	61.6
1 or more	38.4
	(N = 172)
Disposition from Emergency Room:	
Home	52.3
Admit to Medical Service	28.2
Admit to ICU	6.7
Transfer to Psychiatric Hospital	12.8
	(N = 195)

are effective in reducing the rate of suicide attempts and completions among adolescents in Rhode Island.

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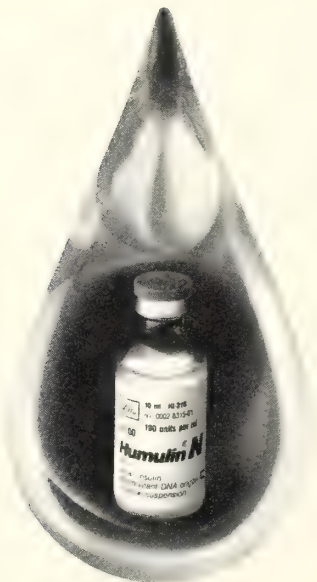
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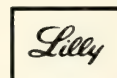


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Influences on Medical Students' Health Beliefs

David B. Reuben, MD

Physicians' personal health beliefs may have a substantial influence in their attitudes and practice of preventive health care.

Introduction

In their role as health care providers, physicians are in a unique position to guide their patients' health habits and behaviors in an effort to prevent illness. Renewed interest in preventive medicine and the increased popularity of Health Maintenance Organizations have been signals that many illnesses are preventable and that health care costs may decline as a result.¹ These concepts have been further reinforced by clinical trials providing strong evidence that rates of heart disease, osteoporosis and hip fractures, lung cancer and numerous infectious diseases can be reduced by appropriate preventive measures.

Before physicians can be expected to fully embrace this movement, they must have a sound knowledge of what preventive health measures are achievable and a belief that patients can modify their lifestyles towards these goals. The question arises as to when and how physicians develop their health beliefs. Perhaps students who believe that people can influence their health are more likely to enter medicine as a career. Alternatively, the educational process of medical school may inculcate the notion that diseases are preventable. The influences of other factors such as personal and family illnesses, relatives who are health professionals and religion must also be considered. Finally, the clinical component of medical school may be important. For example, medical

students who are exposed to patients with lung cancer as a result of smoking may believe that many illnesses can be avoided by good health habits. On the other hand, the effect of caring for children afflicted with leukemia might produce the opposite health belief, ie that fate is responsible for many illnesses and good health is less likely to be a function of self-control.

To begin answering these questions, surveys assessing influences on medical students' health beliefs were conducted before and after their initial clinical training using a well recognized scale of health beliefs.

Methods

All Brown University Program in Medicine students enrolled in the Class of 1987 were administered a one page questionnaire in the spring of 1985 which contained open-ended questions about influences on their health beliefs and the Health Locus of Control (HLC) scale.² At that time, students were completing their preclinical work and none had had substantial clinical exposure during medical school. The same survey was administered again to these students at the time of their Community Health Clerkship, a mandatory clerkship that requires successful completion of the core internal medicine clerkship as a prerequisite. As a result, most students complete their Community Health Clerkship late in their junior year or during their senior year. Although students were requested to write their names on the survey, confidentiality was assured and participation in the study was voluntary.

Open ended responses regarding influences on the students' health beliefs were coded into one of ten categories: medical education/teachings, personal illness, family member's illness, friend's illness, parent's or sibling's occupation,

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religious beliefs, sports/athletics, patients/clinical experience, previous employment, or "other" unclassifiable factors. Up to three responses were coded for each student.

The HLC is a well validated 11 item scale that was developed as an unidimensional measure of people's belief that their health is or is not determined by their behaviors.² The scale is scored such that persons who score high on the instrument are "health externals" who believe that factors that determine their health are such things as luck, fate, chance or powerful others, ie, factors over which they have little control. In contrast, those who score low on the scale are "health internals" who believe that they stay healthy or become sick as a result of their personal behavior. Alpha reliabilities of internal consistency have ranged from 0.40 to 0.72.³ Scores range from 11 (most internal) to 66 (most external) with 38.5 considered as the theoretical midpoint (neither internal or external). The overall scale can also be broken into two subscales (internal and external) which are independent of each other. The external subscale has been reported to have approximately the same alpha reliability as the overall scale and the internal subscale is even higher.⁴ Since its development in 1974, the scale had been used in at least 35 studies in a diverse variety of clinical and experimental settings.⁴ In several studies, the HLC has been used as a dependent variable measured repeatedly to reflect changes in health beliefs following an intervention.

Analyses of data were performed using MacStat's software package. One way analysis of variance was used to compare pooled preclinical to postclinical responses for overall HLC scores, and internal and external subscale scores. For paired responses, paired t tests were performed to compare preclinical to postclinical responses for the same dependent variables. For paired responses, correlation coefficients were calculated to determine the relationship of length of clinical training (in months) to total and subscale scores as well as the change in these scores before and after clinical training.

Results

Of 81 students originally matriculated in the Class of 1987, nine students have yet to enter their senior year of training. Four students took leaves of absence, two were dismissed, and one student each left for the following reasons: dropped out of medical school, transferred to another medical school, and elected not to transfer to Brown after

Table 1. Major Influences on Medical Students' Health Beliefs

<i>Influence</i>	Before Clinical Training % listing influence	After Clinical Training % listing influence
Medical education/ Teachings	28	26
Patients/Clinical experiences	8	28
Religious beliefs	10	10
Family member's illness	4	13
Parent's or sibling's occupation	7	10
Sports/athletics	3	10
Personal illness	4	7
Friend's illness	1	4
Previous employment	3	3
Other influences	48	29

Totals are greater than 100 per cent because students listed more than one influence.

having been accepted. Thus, 72 students completed their preclinical training in the spring of 1985 and graduated in the spring of 1987. Of these 72 students, 63 (88 per cent) completed questionnaires both before and after some clinical training (average 18 months, range 6 to 24 months). An additional four unnamed preclinical responses were returned and nine named post clinical responses were returned providing an overall response rate of 97 per cent. Of the 135 named responses, 85 (63 per cent) were from male students and 50 (37 per cent) were from female students.

The most commonly cited major influence on the medical students' health beliefs before clinical training was medical education/teachings (mentioned by 27 per cent). The most commonly mentioned postclinical influence was patients/clinical experience (mentioned by 28 per cent), although medical education/teaching was still an important influence (mentioned by 27 per cent). Overall, 50 per cent of the postclinical responses listed either medical education/teachings or patients/clinical experience as an important factor. Other major influences on students' health beliefs are listed in Table 1. Although a large percentage of students' responses were categorized as "other" influences, many of these were vague (eg, "personal beliefs," "my family") and could not be classified with any certainty.

The average total, internal and external scores for both pooled and paired samples are presented in Table 2. No differences in any scale

Table 2. HLC Scores Before and after Clinical Training

	Pooled Responses		Paired Responses	
	Before	After	Before	After
Total Score	32.8	33.0	32.8	33.4
Internal Score	19.1	18.7	19.1	18.5
External Score	16.9	16.6	16.9	16.9

None of the differences are statistically significant.

could be demonstrated before and after clinical training. Gender of medical students did not make any difference in the total or internal scores but males scored higher (more external) on the external subscale; average male scores were 17.4 compared with 15.6 for females ($p < .05$). This difference appears to have been established by the time of the first survey because before and after external scores did not differ when controlling for gender. No relationship could be established between the amount of clinical experience (ie, months between before and after surveys) and absolute total or subscale scores or change in total or subscale scores.

Discussion

In this study, the most frequently mentioned influences on medical students' health beliefs were related to medical school. Furthermore, after an average of 1½ years of clinical work, students mentioned clinical experience as an influence more often than any other factors. By this time, 50 per cent of students cited some aspect of their medical education, either preclinical or clinical, as a major influence in their health beliefs. The remaining influences that could be classified fell into four categories 1) personal, family member or friend's illnesses, 2) religious beliefs, 3) sports or athletics and 4) either personal work experience or a relative's occupation. Unfortunately, the relative importance of these items in forming a student's overall health beliefs cannot be gathered from this study. For example, a student who had been treated for a lymphoma may have been profoundly influenced by his disease. On the other hand, another student may have been influenced most by preclinical teachings but this influence may have carried far less weight.

In addition to assessing influences on health beliefs, a measure of Health Locus of Control may be very important in predicting attitudes and practices of preventive medicine. Physicians have been the vanguards of advocacy for personal preventive health in the United States. In

the five year period 1978 to 1983 the smoking rate among Rhode Island physicians fell by one-third. Only 8.3 per cent of physicians now smoke compared to 31 per cent of the general Rhode Island population.⁵ In Massachusetts, physicians are less likely to smoke, drink less and use seat belts more often than lawyers.⁶ As a result of lifestyle modifications, the rate of death from coronary heart disease among white male California physicians fell from being 15 per cent *higher* than age-matched controls in the 1950 to 1954 time period to being 31 per cent *lower* than controls in the 1975 to 1979 time period. The decline in rates for physicians exceeded that for controls by 40 per cent.^{7,8} These healthy behaviors of physicians may yield direct benefit for their patients. Physicians with good personal health habits are significantly more likely to counsel their patients regarding all of their health habits.⁹

Given these healthy lifestyles of physicians, it would be logical to conclude that medical students would be likely to score as "health internals" on a measure of Health Locus of Control. Indeed, the average scores of these medical students (approximately 33) was substantially lower (ie, more internal) than the theoretical midpoint (38.5) indicating internality. As such, medical students' scores, both before and after their initial clinical training, were comparable to undergraduate college students that have been studied using the Health Locus of Control scale. Medical students' scores were substantially lower than those of other populations including unmarried pregnant women, cancer patients, men with coronary artery disease and dialysis patients. On the other hand, medical students' scores were higher than persons who adhered to exercise programs.⁴

Locus of control has been measured in medical students and internal medicine residents.^{10, 11, 12} The focus of these studies has been the relationship of personality traits to stresses associated with preclinical and clinical training. In contrast, the present study specifically examines medical students Health Locus of Control to probe beliefs that might influence their practice of preventive medicine for both their patients and themselves.

Several additional observations are notable. Medical students' scores on the total scale or either subscale did not change before and after their initial clinical training. Similarly, the length of training did not influence the absolute score on these scales or the difference between the two surveys on paired analysis. These findings suggest that medical students' Health Locus of Con-

trol have already been established by the time they enter their clinical years. This conclusion is consistent with data of Dornbush and colleagues who found that first year and third year medical students did not differ on attitude scales regarding preventive medicine.¹³ Scott, et al similarly noted that importance ratings for preventive care did not change over a 30 month period during medical school. Over that period, however, these investigators noted that students had increased confidence in the ability of physicians to provide preventive care.¹⁴ Thus, in spite of the lack of attitudinal change, these studies suggest that students' practice of preventive medicine may be influenced by medical education.

Although our findings begin to explore influences on students' personal health beliefs and potential future preventive health care practices, the results should be interpreted with caution. Despite a near 100 per cent response rate, the survey was completed at only one institution. Thus, the effects of geographic and curriculum differences between medical schools cannot be weighed. Moreover, health beliefs were evaluated at only two points in time. A more extended longitudinal study tracking students from premedical through postgraduate training would provide considerably more information regarding when students' health beliefs are formed. Further research should also attempt to identify which preclinical and clinical components of the curriculum are most influential in formulating students' health beliefs. These courses and rotations can then be targeted as opportunities to discuss personal health beliefs and teach preventive medicine.

In summary, the results of this study emphasize the importance of the medical school in influencing future physicians' health beliefs. Accordingly, good health behaviors for students and their patients should be taught formally and informally in medical school. As students enter the clinical years, their patient encounters emerge as major influences. Faculty should be aware of the importance of these encounters in determining the students' attitudes toward preventive medicine, and possibly incorporating health prevention measures into their future practices.

Summary

Physicians' personal health beliefs may have a substantial influence on their attitudes and practice of preventive health care. To assess influences on these health beliefs and gain further insight into these beliefs, a survey containing open

ended questions and the Health Locus of Control (HLC) scale was administered to an entire class of medical students at the end of their preclinical training and again after an average of 18 months of clinical training.

The most frequent major influence mentioned by preclinical students was medical education/teaching (by 27 per cent) but after clinical training, patients/clinical experiences was cited more often. Although medical students' responses on the HLC were more internal than the theoretical midpoint, they were less internal than persons adhering to exercise programs. Moreover, HLC scores did not change after initial clinical training. These findings suggest that HLC may be established before the clinical years. Nevertheless, medical school has the potential for substantially influencing health beliefs.

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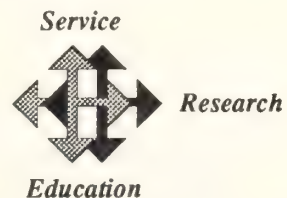
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HARD CHOICES: Medical Ethics, Law and Health Policy

Edited by Edward N. Beiser, PhD, JD

The Discontinuation of Life-Sustaining Treatment

About five years ago, I was the guest of the Department of Medicine at one of the University of California teaching hospitals. During morning rounds, we came to the bed of a patient who had previously requested that he not be intubated should he develop cardiac arrest. As the team of physicians discussed the case, I asked, "Do you write 'DNR' orders in the chart?" The chief resident looked at me as though I had asked something roughly as stupid as, "Do you scrub before surgery?" He then patiently explained to me the hospital's procedures for determining code status which entailed formal discussion with the patient and his family, careful documentation in the chart, and regular review. From the perspective of this house officer, I had asked a singularly dumb question, since in every institution in which he had trained there had been a formal method for determining and recording code status. With typical lack of historical perspective, he failed to recognize that at that very moment major medical centers elsewhere had no formal "Do Not Resuscitate" policies because they had been advised by counsel that it was not legal to withhold life-sustaining treatment from a patient.

Many who read this column will recall that when they were in residency training the designation of certain patients for less than a "full court press" was a highly informal matter. Some hospitals employed erasable lists at the nursing station. Others placed a special sticker [a blue or purple dot] on the chart. Word of mouth among house staff identified those patients who would receive a "slow code" or a "Hollywood code." Only in recent years have the hospitals of Rhode Island formalized their policies for the determination of code status. Initially what was required was a mere "yes or no" determination of whether to resuscitate; the second generation of questions with which our hospitals now grapple are better captured by the phrase "stratification of care," and involve the issue of what treatment modalities, if any, may be withheld.

Indeed, despite the naive certainty of this California chief resident that things which are familiar to him are universally accepted, there are

Rhode Island physicians who will not sign a "Do Not Resuscitate" order at the very time that a federal court in this state ordered the discontinuation of Marcia Gray's feeding tube [see discussion in RIMJ Sept. 1989, pp 335-337].

In many institutions, pressure for a formal, written code-status policy had originated from the nursing staff. When in the middle of the night duty nurses were confronted with an acutely ill patient they wanted unambiguous instructions as to how aggressively they were expected to react. Certainly the practice of ethical medicine is enhanced by the regular formal procedures, including an explicit definition of who is responsible and a written notation in the chart of something as important as whether CPR may be withheld. If withholding of treatment grows out of an ethical respect for the patient's autonomy [or for the wishes of the family of the incompetent patient], it becomes vital that such wishes be ascertained carefully and precisely, and that an attending physician take responsibility for formalizing the order. Informal, seat-of-the-pants, evaluation of how aggressively to treat a patient would be hard to defend.

The establishment of formal, regularized procedures for the determination of code status in particular, or for the stratification of care in general, may be essential for the practice of ethical medicine. Such procedures, however, cannot eliminate the difficult questions which remain. Marcia Gray's care presented two vexing questions: Is there a difference between the withholding of and the withdrawal of medical treatment? And, is there a difference between withdrawal of life sustaining treatment and suicide?

Is there a difference between the withholding of and the withdrawing of medical treatment? A resident physician at a Brown-affiliated hospital, late one night, was called to the bedside of a patient whom he did not know. The patient suffered from advanced cancer with extensive metastases, and the question arose as to whether the patient should be intubated. The chart contained no indication of a code status. [Presumably every patient is a

"full-code" unless otherwise noted.] Because of the seriousness of the patient's underlying disease, the cross-covering house officer suspected that a DNR order might be appropriate and accordingly he attempted to contact the patient's private physician by telephone. He was unable to reach the attending physician but did reach his partner who did not know the patient well enough to be helpful. [The situation of a cross-covering resident physician speaking to a cross-covering attending physician in the middle of the night is a compelling argument in favor of planned discussions, with certain patients, regarding code status and other treatment options.] It was decided, in this case to call the family; and late that night the resident physician telephoned the patient's daughter, explained the situation and told her that he needed a decision within ten minutes.

The daughter's response to this request strikes me as absolutely proper: She told the resident physician to start the ventilator and that she would come in with her brothers and sisters at a decent hour the next day and then sit with the concerned physicians in order to make intelligent decisions.

The resident physician refused to accept this solution. His view was that the family could instruct him to withhold treatment — to refrain from placing the patient on the ventilator. But, he argued, once you began — once you had the tiger by the tail, so to speak — you could not let go.

In my opinion, the attitude of this resident physician — which certainly represents commonly held wisdom in the hospitals of this state — is not only wrong, but dangerous. It is likely to lead to inappropriate medical judgments, and it is likely to lead to inappropriate ethical judgments.

Medical students commonly believe that withdrawing or discontinuing treatment is "active," whereas refraining from instituting treatment is "passive." I suggest that this is a word-game without moral meaning. Any situation which can be described as "passive" can be equally construed as "active."

If a physician writes the words "do not intubate" within a chart, I see no merit in calling that transaction "passive." If a house officer notices that a thrashing patient has pulled out his tube, I see no point in calling it "passive" when he walks on without replacing the tube, but calling it "active" were he to clamp the tube. The decision not to prescribe an antibiotic for the elderly patient's

pneumonia is just as "active" as the decision to discontinue an antibiotic which has been administered.

Some would say that it is sometimes morally permissible to withhold penicillin from a patient with an otherwise treatable pneumonia if, for example, the patient were ill with some independent, irreversible disease. [Pneumonia had once been called "the old man's friend."] Others would state that it is never permissible to withhold a potentially efficacious therapy. My point here is that from either moral posture, there is no difference between not beginning penicillin and deciding to discontinue its use once begun. If it is morally proper to withhold penicillin for the explicit reason of permitting the patient to die of his pneumonia, then it is just as morally permissible to discontinue penicillin for the same reason. The physician who writes the first order — withhold penicillin — is no more or less "active" than the physician who writes the order to discontinue.

The resident physician who believed that it was possible to refrain from placing a patient on the respirator but impossible to remove him may well have been reflecting the political realities in his hospital. Certainly physicians feel that they are less likely to get into trouble for what they refrain from doing than for what they are perceived as undertaking. But this simply means that hospital administrators and the general public need to understand that the distinction between the withholding and the withdrawing of treatment is illusory.

As a matter of law, Judge Boyle's opinion in the Marcia Gray case is totally unambiguous on this point:

"No analytic difference exists between withholding and withdrawing medical treatment, however. A patient's right to refuse medical treatment obviously includes both the right to refrain from beginning the treatment and the right to order its cessation."

Thus, legally, it is no more improper to discontinue treatment in Rhode Island than it is to fail to initiate that treatment. Of course the opposite is equally true: If there is a duty to provide care, it is as much a violation of that duty to fail to provide care as it is to discontinue care once begun.

It is truly unfortunate that many health care professionals continue to advocate the "tiger by the tail" attitude: Namely, that once you begin a treatment modality, you may not discontinue it.

From the vantage point of good clinical medicine, that attitude is likely to force physicians to make decisions prematurely, with less than complete data. The courts, with much sensitivity, have come to recognize this:

"From a policy standpoint it might be unwise to forbid persons from discontinuing a treatment under circumstances in which the treatment could permissibly be withheld. Such a rule could discourage families and doctors from even attempting certain types of care and could thereby force them into hasty and premature decisions to allow a patient to die." [Judge Boyle, in *Gray v. Romeo*, as quoted from the New Jersey Supreme Court in *In re Conroy*.]

The physician in the emergency room who can at best only dimly predict the patient's likely course of progress should not be forced to make treatment decisions based on the fear that in two weeks it may be impossible to wean the patient from the ventilator. The resident physician confronting a thrashing patient in the middle of the night ought not be forced to make decisions with limited available information because of his fear that when the CT scan or the laboratory results become available it will then be too late, for political reasons, to discontinue treatment.

From an ethical standpoint there may indeed be situations where a family must be called in the middle of the night and told that a treatment decision must be made within ten minutes. But never, I suggest, for fear that if we begin to treat, they won't let us stop, later.

The reaction of the family member in the case cited above — begin the ventilator now and I will come to the hospital at 10 am with my brothers and sisters, and we will then figure out what is best — was eminently sensible. Judge Boyle's decision in the Marcia Gray case, that there is no distinction between withholding and withdrawing treatment, would have protected the resident physician and the hospital's ability to provide both good clinical medicine and morally responsible medicine to this patient. Forcing a decision by a resident physician and an attending physician, both of whom were cross-covering, as well as an overwhelmed family member, for fear that if they placed the patient on the ventilator they would never be permitted to disconnect him, serves nobody's best interest.

Food for thought: What, if any is the connection between discontinuation of life-sustaining care and euthanasia or even suicide?

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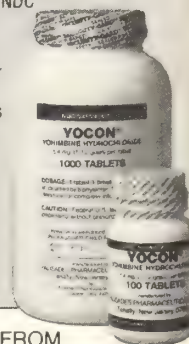
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References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
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Chronic Obstructive Pulmonary Disease Mortality in Rhode Island

Chronic Obstructive Pulmonary Disease (COPD) is the fourth leading cause of death in Rhode Island (following heart disease, cancer, and cerebrovascular disease). COPD encompasses a group of conditions characterized by chronic airway obstruction or slowing of forced expiratory flow, and includes chronic bronchitis, emphysema, and asthma. The risk of death from these conditions rises generally with age, from a low of 0.4 per 100,000 for those under 35 years of age to 373.3 per 100,000 for those aged 85 or older in 1987 (Fig. 1). The relative risk (RR) of COPD for males (vis-a-vis females) is significantly higher at ages 65 or above. In the age group 75-84 years, for example, RR = 2.8 in 1987.

Approximately 82 percent of COPD mortality can be attributed to smoking.¹ Despite falling percentages of the smoking population, however, COPD mortality has been rising. From 1980 to 1987, smoking prevalence fell 29 percent, from 34 to 24.3 per 100,² while age-adjusted COPD mortality climbed 17 percent, from 24.9 to 29.2 per 100,000. The independence of these two trends has been attributed in part to the long latency between smoking onset and death from COPD.³

In Rhode Island, the increase in COPD mortality independent of age has been apparent for both females and males (Fig. 2). For females, the age-adjusted death rate rose an average of eight percent annually between 1980 and 1987. Among males, the corresponding increase was two percent per year.

Figure 3 showed that age-adjusted death rates for bronchitis, asthma, and emphysema fell slightly between 1980 and 1987. All other conditions of COPD (primarily unspecified chronic airway obstruction) rose 36 percent during this time.

References:

1. Centers for Disease Control (CDC), Chronic Obstructive Pulmonary Disease Mortality — United States, 1986, Mortality Morbidity Weekly Report (MMWR) 1989:549-552.
2. Rhode Island Department of Health (RIDH), unpublished data from Behavioral Risk Factor Surveillance System, 1989.
3. Centers for Disease Control (CDC), Chronic Disease Reports: Mortality Trends — United States, 1979-1986,* (MMWR) 1989:189-193.

Figure 1. Chronic Obstructive Pulmonary Disease Death Rate by Age and Sex, Rhode Island, 1987

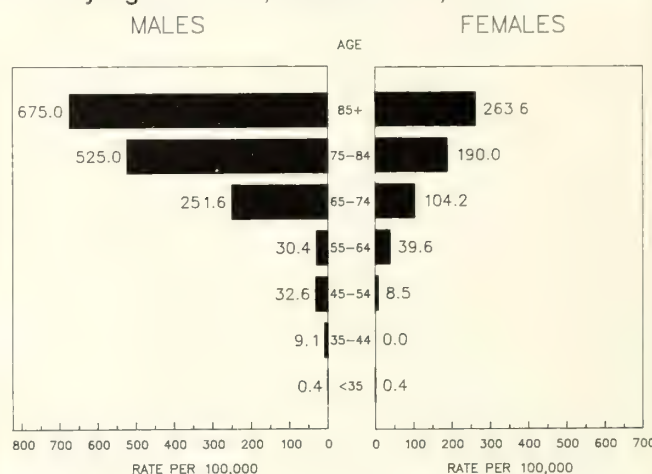


Figure 2. Age-Adjusted Chronic Obstructive Pulmonary Disease Death Rate by Sex, Rhode Island, 1980-1987

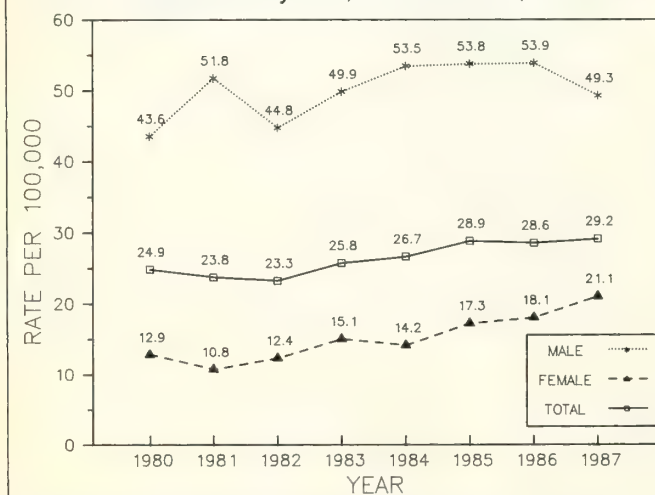
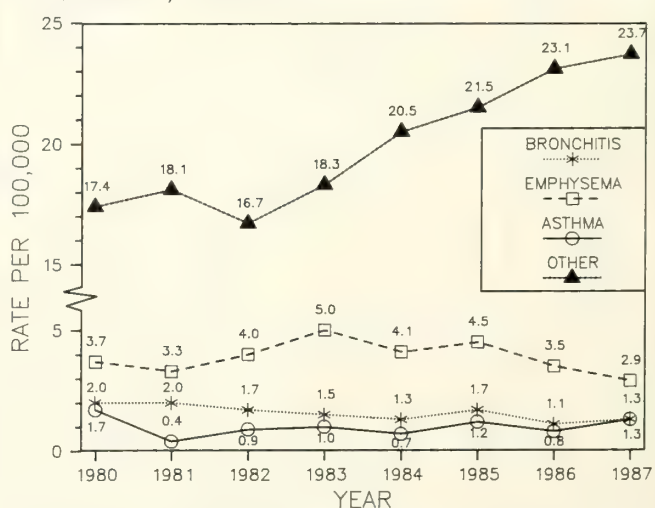


Figure 3. Age-Adjusted Death Rate for Specific Conditions of Chronic Obstructive Pulmonary Disease, Rhode Island, 1980-1987



R H O D E S T A T E O F I S L A N D Monthly Vital Statistics Report

Provisional Occurrence Data From the Division of Vital Records

H. Denman Scott, MD, MPH
Director of Health

Roberta A. Chevoya
State Registrar

Vital Events	Reporting Period	12 Months Ending with July 1989	
	July 1989 Number	Number	Rates
Live Births	1,392	14,953	15.1*
Deaths	707	9,688	9.8*
Infant deaths	(20)	(143)	9.6†
Neonatal deaths	(16)	(109)	7.3†
Marriages	803	8,341	8.4*
Divorces	248	3,755	3.8*
Induced Terminations	667	8,005	535.3†
Spontaneous Fetal Deaths	97	1,132	75.7†
Under 20 weeks' gestation	(90)	(997)	66.7†
20 + weeks' gestation	(7)	(114)	7.6†

*Rates per 1,000 estimated population.

†Rates per 1,000 live births.

Underlying Cause of Death Category	Reporting Period	12 Months Ending with April 1989		
	April 1989 Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	290	3,580	360.5	5,100.5
Malignant Neoplasms	183	2,425	244.2	7,749.5
Cerebrovascular Diseases	45	615	61.9	994.0
Injuries (Accident, Suicide, Homicide)	39	434	43.7	9,659.0
COPD	26	316	31.8	444.5

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 current estimated population of 993,000.

(c) Years of Potential Life Lost (YPLL)

NOTE: Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

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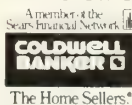


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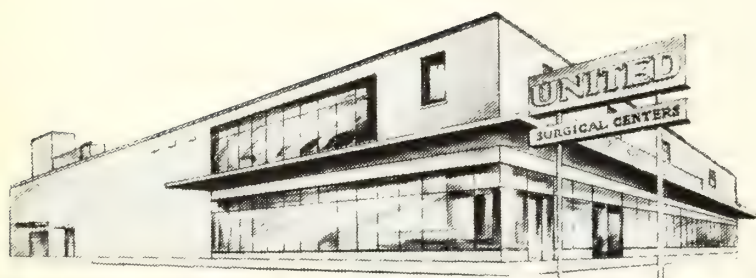
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THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

Fifty Years Ago (November, 1939)

The lead article on obstructive uropathy is written by Alexander Randall, MD, Professor of Urology at the University of Pennsylvania and was initially read at the Intern Alumni Day meeting of Memorial Hospital in Pawtucket. Dr Randall discusses the many new and marvelous diagnostic methods and therapeutic measures, the newer physiology of renal function, the rapid strides in blood chemistry determinations and the refinements in pyelography as they pertain to obstructive diseases of the urinary system.

In summary, Randall states:

"1. That intravenous methods for urologic diagnosis have changed our point of view from terminal pathology in the organs to a physiological study of the urinary system and urine transportation.

2. That the physiological transportation of the urine is the basic essential factor to the early understanding of this problem.

3. That the slowly developed and chronic obstructions characteristically give gastrointestinal symptoms, and that every chronic abdominal complaint should receive the advantages of an intravenous urographic study.

4. That red blood cells in the urine demand an explanation.

5. That the treatment of unilateral kidney infections by drugs demands, besides recognition of the organism and choice of the specific drug, sufficient renal function for a therapeutic effect.

6. That we are approaching a realization that certain cases of hypertension have a unilateral renal etiology amenable to surgery."

The second article in the November 1939 issue of the *Journal* is written by Paul W. Preu, MD, and is concerned with bromide intoxication. On

the basis of 18 instances of bromide intoxication (encountered by the author in 2,000 consecutive admissions to the psychiatric inpatient service of the New Haven Hospital) the following essential observations are shared with the reader:

"1. Bromide intoxication is a serious but preventable condition.

2. Bromide intoxication is manifested by psychiatric or dermatologic symptoms which may occur alone or together. The diagnosis is confirmed by the demonstration of a toxic concentration of bromide in the blood.

3. The tendency of bromide to displace chloride and to accumulate in the tissues is the decisive factor in the production of intoxication.

4. Dehydration and dietary deficiency are important contributing factors.

5. Treatment of the intoxication depends on the administration of adequate amounts of fluids and chlorides.

6. Bromide should be used less frequently in medical practice, and only under continuous medical supervision.

7. The sale of bromide without a physician's prescription should be prohibited."

This issue of the *Journal* carries an editorial on surgery in patients with heart disease. On the basis of recent observations in the medical literature and personal experience, the following frequency rates and conclusions are offered: "Four hundred and fourteen patients with heart disease who underwent 494 operations were studied. The total mortality was 13%. There were 147 operations on patients with valvular disease with a mortality of 2.1%. One hundred operations on patients with auricular fibrillation carried a 3% mortality. Forty-one operations on patients with coronary thrombosis resulted in a mortality of 44%. Most of these deaths occurred in patients with recent coronary thrombosis.

Thirteen operations on patients with syphilitic aortitis resulted in a mortality of 9.1%. Six operations on patients with paroxysmal tachycardia carried no mortality. Fifty operations on patients with congestive heart failure resulted in a mortality of 17%. Four hundred and thirty-three operations on patients with heart disease without nephritis carried a mortality of 4.9% while 61 operations on cardiacs with nephritis showed a mortality of 14%."

At a stated meeting of the House of Delegates of the Society, it was voted that a committee of three be appointed to cooperate with Dr Jesse P. Eddy, III in the formation of a Blood Donors League in Rhode Island. The delegates also voted that Dr Alex M. Burgess be appointed to confer with Senator Theodore Francis Green urging him to support a congressional appropriation for the Army Medical Library and Museum in Washington.

Twenty Five Years Ago (November, 1964)

The lead article is written by Alton M. Paull, MD, and is entitled, "Sheehan's Syndrome with Myxedema Crisis." A patient with typical Sheehan's syndrome with myxedema crisis is reported. "In spite of sixteen years of a miserable existence, an excellent response to therapy was obtained with replacement therapy. In view of the high incidence of this complication in obstetrical shock, all patients whose deliveries have been complicated should be aggressively followed for at least a year to be certain that the syndrome does not develop."

On the twenty-fifth anniversary of Rhode Island Blue Cross, a paper is given by Walter J. McNerney, President of the Blue Cross Association, Chicago, entitled "The Rise of the Articulate Consumer." The article notes: "... the hospital system in the country is an extremely successful one. The number of beds per thousand population has grown; the use of these beds has increased; and the number of people taking care of patients has grown appreciably." Further, "In this same period we saw a prodigious growth in prepayment to the extent that now 75% of the population is covered, and we have seen a prodigious growth in the depth of that coverage." And, "Combined with better housing and better diet, these factors have led to lower mortality and morbidity rates."

The author concludes: "I would end by congratulating the Rhode Island Blue Cross as one of the most distinguished plans in the United States. I would call upon it in the sense of a challenge to develop immediately in conjunction with hospitals a planning mechanism such as I have suggested and to give leadership to the concept of review of utilization in the public interest. . . . I call upon it to make it clear to the State as well as to the Federal Government that it is willing to serve in an administrative function in regard to programs like the Medical Assistance to the Aged Program. I call upon it to step forward, announce itself as a renewed partner in this community for the next 25 years."

An editorial entitled, "Race for the Moon not a Stunt" quotes Wernher von Braun in his October, 1964, address to the American College of Surgeons. He states that Project Apollo, the moon shot, "... is not an adventurous race to the moon for dramatic propaganda purposes." He continues: "One recent NASA development is an instrument which will permit precise detection of the effects drugs will have on the heart action of unborn babies. The machine is so sensitive that it is capable of measuring the heartbeats of a bobwhite embryo, without breaking the shell of the egg or implanting electrodes. Also in the works is an improved biotelemetry which can sense and send out signals of the heart beat and respiration of humans."

A book review of Rashevsky's "Some Medical Aspects of Mathematical Biology" derives the following quotation from the text: "The largest computers contain something like 10^5 elements. The human brain contains 10^{13} neurons. It takes a couple of years to build a large computer. At that rate of production it would take about 10^8 years to build a computer equal in its ability to the human brain. Won't the human brain develop during that period about as much as it did in the preceding 100,000 years? If so, the computer, by the time it is built, would be obsolete!"

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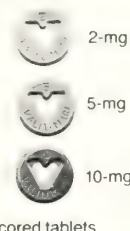
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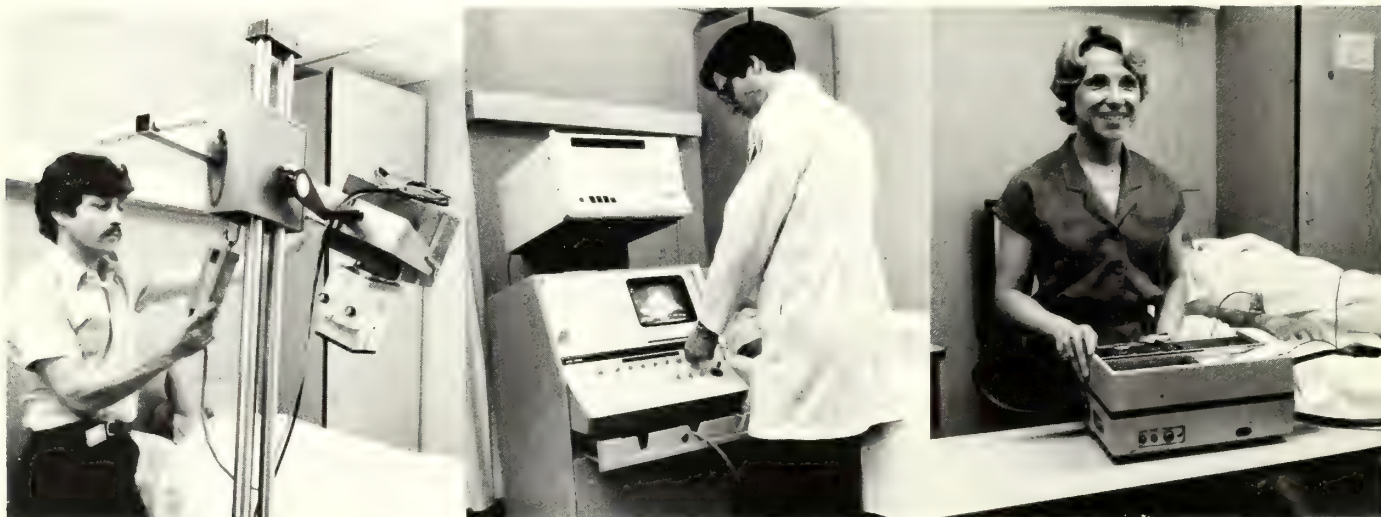
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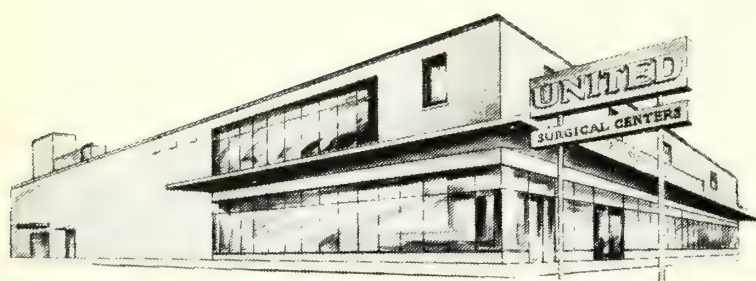
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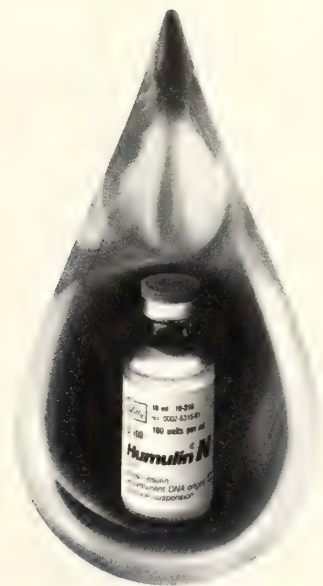
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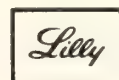


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RHODE ISLAND MEDICAL JOURNAL

The Medical Response to Drinking

"If all be true that I do think," said Aldrich some three hundred years ago, "*There are five reasons we should drink.*" Perhaps so, but there are at least five hundred sobering reasons for considering the alternative, sobriety. Yet another poet, A. E. Robinson, harbored less romantic thoughts of drinking. In 1910 he wrote: "*Miniver Cheevy, born too late, Scratched his head and kept on thinking; Miniver coughed and called it fate, and kept on drinking.*" We recognize alcoholism as a sad participant of a substantial fraction of emergency room admissions and the abuse of alcohol fosters chronic disease, family violence and breakup, accidental injury and death; and in economic terms, falling productivity. By any criterion, the harvest of alcoholism represents an overwhelming public health problem.

In response to this challenge, Brown University in 1982 established its Center for Alcohol and Addiction Studies. From its inception the Center has been imaginatively directed by David Lewis, MD, Professor of Medicine and Community Health at Brown's medical school and one of the leaders of the Association for Medical Education and Research in Substance Abuse (AMERSA), a national organization of scientists, educators and clinicians concerned with chemical dependencies.

The Center now has a faculty of over 40 clinicians, educators and scholars and maintains a research and education program at the Center and in nine hospitals within Rhode Island. During the last year, for example, the Center has accomplished or initiated the following:

- Developed a major treatment-outcome research project to begin in the autumn of 1989, and supported by federal funding in excess of \$3.5 million.

- Developed a training program for physicians where basic knowledge and skills in the diagnostic and therapeutic management of patients with alcohol problems or other dependencies are shared. Various educational modules and curricular designs have been assembled, including video tapes, for distribution to medical schools and hospitals throughout the United States. External funding of about \$400,000 has been

awarded to the Center so that its staff may implement this ambitious educational project.

- The Center now edits a nationally distributed publication, *Substance Abuse* as well as the *Brown University Digest of Addiction Theory and Application*, a publication subscribed to by over 3,000 libraries, clinics and hospitals.

- The Center supervises a post-doctoral training and research program on substance abuse and clinical intervention headed by Professor Richard Longabaugh and Dr Lewis. This program is designed for behavioral, medical and social scientists pursuing a career in chemical dependency research. There are eleven scientists presently in training. Current research projects undertaken by the Center's fellows include: an analysis of substance abuse by battered and homeless women, leading to the probable establishment of a shelter for such persons; an assessment of dependency prevention programs for South East Asian youth in Rhode Island; studies on adolescent substance abuse; studies on factors associated with relapses; studies on sensation-seeking use of alcohol in children and adolescents; studies on the pharmacokinetic interactions between alcohol and methadone; and the effects of calcium channel antagonists on morphine tolerance and dependence.

- Collaborative studies in cooperating hospitals (Roger Williams General Hospital, Miriam Hospital, Butler Hospital, VA Medical Center) and the Department of Health, supported by extramural funding of over \$1.2 million.

The current issue of the *Journal*, under the Guest Editorship of Dr David Lewis, contains two articles describing detoxification and community training programs, and two papers of more personal concern and personal meaning to practicing physicians: a paper by Rakatansky on avenues of assistance for the chemically dependent physician; and an article by Donovan on self-help programs for physicians.

Stanley M. Aronson, MD

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Physicians Can Help the Addicted

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... we must expand our understanding of how alcohol and drug dependencies are begun and what resources are available to reach a drug-free, sober state.

Physicians can play a vital role in the lives of patients with addictive problems by helping them to understand their behavior and showing them how to attain and maintain recovery. To achieve this, we must expand our understanding of how alcohol and drug dependencies are begun and what resources are available to reach a drug-free, sober state. In this issue of the *Journal* we explore the three dimensions (chemical, personal, environmental) through which we have come to perceive drug abuse and addiction. These three dimensions interact in the common ground of repeated drug-taking behavior and the transition from occasional drug use to chemical dependence.

Each addictive chemical is unique, and as we gain more information about neuroreceptors and neurotransmitters, we will better identify the neural sites of chemical action, thus opening the way to the design of specific and effective pharmacotherapies. Detoxification is not an exclusively chemical enterprise; personal factors contribute materially to the individual variation in therapeutic effects. This dimension is explored in Wartenberg's article concerning the Roger Williams General Hospital program.

The unique nature of the person interacting with the drug is yet another important determinant. The personal dimension includes such

factors as personality type, body weight, nutrition, prior drug use, drug-effect expectations, and family history of addiction.

The effects of the environment in influencing behavior — culture, peers, community education, law enforcement — are more important than is generally believed. The relevance of environmental influence underlies the unique prevention project reported in this issue by the group from the Rhode Island Department of Health. Their study seeks to clarify those interventions which may diminish alcohol-related trauma.

Professor Bruce Donovan's article on Alcoholics Anonymous (AA) serves to lessen many of the misconceptions surrounding this private group and describes the personal issues that an individual must address in relating to AA. Dr Herbert Rakatansky's important article describes the rigorous interventions undertaken by the Rhode Island Medical Society's Impaired Physicians Committee and illustrates by case reports the unusual effectiveness of these measures.

Mysteries remain in our understanding of human addiction; not the least of these is the chemically dependent person's appetite to continue alcohol or drug use despite irrefutable evidence of personal, career and family harm. This is frustrating to physicians and family. How then is recovery established? Dr James Prochaska at the University of Rhode Island has developed a model which helps in analyzing the behavior of an addict as he frees himself of addiction. This model explores the readiness of the addict for

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change and has been employed in studying persons who have given up cigarette smoking. The sequential steps in this readiness for change model are:

PRECONTEMPLATION

Is not considering change. May not be convinced that the behavior is a problem.



CONTEMPLATION

Thinks seriously about changing behavior.



ACTION

Takes positive steps towards changing behavior.

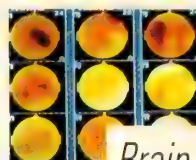


MAINTENANCE

Maintains the behavior change.

Physicians can contribute materially within the framework of this "Readiness for Change" model. Brief advice or continuing support may be all that is needed. For the more seriously affected, the physician should refer the addicted patient to one of the many competent treatment resources in the state of Rhode Island. In any case, buttressed by knowledge of the chemicals, the person, and the environment, physicians can be effective in the prevention of addiction or the care of those already addicted.

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Addiction in Doctors: Hope and Help

Herbert Rakatansky, MD

Effective mechanisms and avenues for treating chemical dependency in the doctor have been devised and employed in Rhode Island.

There have been many articles on the dynamics and treatment of alcohol and drug addiction, but, until now, few papers have addressed addiction in the care-giver, and specifically the interface between the addicted doctor (whether physician, osteopath, dentist or podiatrist) and the larger society. Effective mechanisms and avenues for treating chemical dependency in the doctor have been devised and employed in Rhode Island. These mechanisms serve to protect the public while providing therapy and rehabilitation for the addicted doctor. This paper illustrates and describes these efforts.

Case 1: The physician-in-charge of a free-standing clinic called the Rhode Island Medical Society (RIMS) Impaired Physician's Committee, a committee of physicians charged both with protecting the public from impaired physicians and assisting impaired physicians into treatment. This physician requested help for a colleague who had appeared for work apparently intoxicated. He (all pronouns in this article will be masculine without implying any gender bias) said that this doctor had been thought to be intoxicated on several previous occasions.

Fact: Doctors are at least as susceptible to addiction as the general public. They develop alcoholism at the same rate as non-physicians but have a higher rate of drug addiction, perhaps because of the ready availability of controlled drugs.¹ The Committee accepts referrals from any person, including physicians, family members, patients and friends, but does not accept anonymous referrals.

Case 1 (cont.): The physician-in-charge of the clinic was advised that he would receive a call for a confidential discussion. During the ensuing discussion the physician expressed a desire to confront the intoxi-

cated doctor and refer him for treatment. Since most alcoholics are in denial about their addiction, the physician was advised that without a structured format and some kind of leverage it was unlikely that the contemplated intervention would succeed.

Fact: All addicts, and particularly doctors, deny their addiction. Alcohol and drug-addicted doctors tend to use their substances in isolation, except perhaps cocaine which may be used in social settings. They tend to preserve their professional practices at the expense of other parts of their lives such as family and community activities. Furthermore, they rarely discuss their addiction with anyone for fear of jeopardizing their professional status. Thus, typically, they have neither the support of others nor an awareness of channels for help.

Other physicians with little knowledge of the nature of addiction often harbor negative moralistic views of the addict and tend to ignore the addicted physician until his behavior is so flagrant as to constitute a gross danger to others. Intervention with an addicted doctor requires a sensitive skill no less demanding than that required for the treatment of any other behavioral or physical illness.

Case 1 (cont.): The physician at the clinic, nevertheless, planned to intervene personally but when the doctor appeared at 9 AM the next day obviously intoxicated he called for assistance. The doctor was confronted by members of the Impaired Physicians Committee several hours later. He was, in their judgment, grossly intoxicated and a clear threat to his patients were he to return to work. A suggestion that he enter a treatment program was met with intense resistance. However, he consented when told that he would be reported to the Health Department if he did not enter the hospital, with the recommendation that his license be suspended. The hospital had been contacted previously and a bed was being held. He was then driven

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ABBREVIATIONS USED:

AA: Alcoholics Anonymous

MAST: Michigan Alcohol Screening Test

NA: Narcotics Anonymous

RIMS: Rhode Island Medical Society

to the hospital with no stops. Upon arrival at the hospital, about four hours after his last drink, his blood alcohol level was over 400 mgm per cent. The interval between the initial phone call and the arrival at the hospital was four hours.

Fact: *Structured confrontation with leverage is a proven method of convincing doctors to enter treatment.*

If the evidence for alcoholism had not been convincing or had there been a doubt about whether addiction was indeed a problem, the doctor would have been asked to get an independent evaluation. This would have been offered by physicians specializing in addiction who are not members of the Committee. A protocol has been established which defines the nature of the evaluation (see table). The results of the evaluation would then have been reviewed by the Committee which might then have:

- (1) closed the case, had the report revealed no evidence of addiction,
- (2) asked for further evaluation based on the suggestions of the consultant, or,
- (3) confronted the doctor again, had the report been suggestive of addiction.

If the doctor had refused to be evaluated, the Committee would then have considered whether the evidence prompting the confrontation was sufficient to justify a report to the Board of Licensure. If so, a report would then have been promptly submitted. The original complainant, in every case, is informed of his right to file his own complaint with the Board.

Case 1 (cont.): After a period of detoxification the patient was admitted to an inpatient rehabilitation program. During the initial hospital stay the patient continued to deny that he had a significant problem and wished to be discharged and return to work. Continued reminders that any termination of treatment would result in a report to the Board motivated him to stay in treatment. Following discharge he signed an aftercare agreement for an initial period of three years.

Fact: *Doctors respond well to treatment for addiction. The five year response rate is 85-90 per cent, primarily because motivation is good. Doctors who are coerced into treatment seem to do as well as those who enter voluntarily.² Referring a doctor suspected of addiction for evaluation and help is an act of caring and may save both a career and a life.*

Case 2: A 48-year-old doctor was referred to the Committee because of a suspicion of alcoholism. Interview with the doctor revealed that he had been treated previously for alcoholism and recently had resumed intermittent drinking. There was no evidence of im-

pairment at the time of the confrontation. He agreed to enter our aftercare program. Hospitalization was not suggested although the doctor understood that another slip would trigger a course of inpatient therapy.

Fact: *Careful aftercare and monitoring are absolutely necessary for successful recovery. Both case 1 (after discharge from the hospital) and case 2 signed agreements with the Committee specifying the following:*

- (1) *The doctor will select a personal physician and will write no prescriptions for himself.*
- (2) *The doctor will abstain from all mind-altering drugs, including alcohol, unless prescribed by his physician.*
- (3) *The doctor will continue in drug and/or alcohol counselling, usually once a week.*
- (4) *The doctor agrees to attend a specific number of AA or NA meetings, typically two to seven per week.*
- (5) *The doctor will attend weekly meetings of a professionally conducted therapy group for addicted doctors. These groups are led by a psychiatrist certified in addiction therapy but who is not a member of the Committee.*
- (6) *The doctor agrees to random urine testing, twice weekly at the start.*
- (7) *The doctor agrees to release to the Committee information relative to his progress in treatment.*
- (8) *The doctor agrees that the Committee may release information to an Impaired Physicians Committee in another state if the doctor should move during the duration of the agreement.*
- (9) *The doctor understands that if the contract is broken or if suggestions for increased intensity of treatment are not accepted, the state Board of Licensure will be notified.*

The Committee, in return, agrees to:

- (1) *Name one member of the Committee as an advocate for the doctor who will maintain regular contact.*
- (2) *Represent the doctor before any credentials committees and Boards of Licensure (such advocacy almost always is successful).*

Structured confrontation with leverage is a proven method of convincing doctors to enter treatment.

The duration of the agreement is three years with options for renewal by either party. In Rhode Island, over 50 doctors have signed this agreement, with 25 in effect at the time of this writing. A number of doctors have referred themselves after their initial treatment in order to sign the agreement and thus gain the advocacy of the Committee. This aftercare agreement is absolutely essential to recovery and is probably the reason why doctors have such a high rate of recovery.

Case 3: A 33-year-old physician was referred to the committee because he had written excessive numbers of prescriptions for his family and because there was a deterioration in the quality of his practice. An in-

Table — Protocol for Evaluation of Possible Chemical Dependence by RIMS Impaired Physicians Committee

Chemical dependence evaluation to be undertaken by a physician selected by the Committee. At least one further independent evaluation to be provided by a person selected by the primary evaluator. This person may be another physician or someone with appropriate training such as a certified alcoholism counselor. These evaluations, at the minimum, will include:

- drug and alcohol history
- developmental history
- interview with spouse and/or significant others
- MAST questions
- psychiatric history and formal evaluation

Committee will provide all information to the primary evaluator and necessary information to the internist.

Evaluation by an internist who will report directly to the Committee which, in turn, will forward results to the primary evaluator. Internist evaluation, at the least, will include:

- medical history
- physical examination with special note of alcohol or drug effects such as liver disease, needle marks, nasal damage, etc.
- laboratory data, at the minimum to include: comprehensive blood chemistry profile with liver function studies; bloodcount with mean corpuscular volume; toxic screen of both urine and blood.
- EKG, chest X-Ray or other studies deemed necessary by the internist.

The primary evaluator will review all material and make a recommendation to the Committee, in one of the following categories:

- high probability of chemical dependency
- inconclusive evaluation. (In this case the evaluator should state reasons why results are equivocal and make suggestions for further evaluation.)
- low probability of chemical dependency

interview disclosed that he had been writing prescriptions for his wife. He was significantly disturbed by his marital problems and by the illnesses, both addictive and physical, of his wife and accordingly could not function efficiently. He was instructed to cease writing prescriptions for his wife and he was referred for psychiatric counselling as well as to Al-Anon. Shortly thereafter he lost his job and was referred to the Impaired Physicians Committee in his new locality. He was integrated into counselling and Al-Anon. This physician underwent a successful rehabilitation and the Committee received a letter from him several years later expressing appreciation for this intervention.

Fact: A phenomenon called co-dependency can be as serious an illness as the addiction itself. Living with an addict or growing up in an alcoholic (or drug-addicted) household produces behavioral changes which impair healthy functioning. A doctor who has grown up in an addicted family or whose spouse or child are addicted can neither maintain healthy relationships nor practice efficiently. Denial in the co-dependent is even stronger than in the addict. The co-dependent invariably blames the addict. "If only he would stop drinking everything will be OK!" In fact, with appropriate help,

the co-dependent can recover whether or not the addict continues his dependency.

Counselling and participation in Al-Anon are the basis of treatment for the co-dependent. Al-Anon is a support group for friends and relatives of addicted persons but not for the addicts themselves. The Impaired Physicians Committee is eager to help those physicians who confront addiction as a family rather than as a personal problem. Referral of the addicted person to a quality treatment program and help with the issues of co-dependency are our objectives.

Addiction in the health professions is obviously not confined to physicians in private practice. Medical students and resident physicians are equally vulnerable. Residents who are identified in the training institution are handled by our Committee. Cooperation of the program director, of course, is essential. The medical student community at Brown University has recognized the problem of chemical dependency and has formed an Impaired Students Committee which functions in cooperation with the RIMS Committee.

Referring a doctor suspected of addiction for evaluation and help is an act of caring and may save both a career and a life.

The RIMS Impaired Physicians Committee is organized as a peer review group under Rhode Island law. This structure insures immunity both to its members and to those who report to the Committee so long as they act in good faith. All records are kept confidential, are not subject to subpoena, and are not released without the written consent of the patient. Records of the Impaired Students Committee are kept off campus at the RIMS offices, thus removing any possibility of access to them by the University administration.

Summary

A successful mechanism providing structured assistance and therapy for addicted doctors and medical students has been established in Rhode Island. It is critical that physicians, their families, patients and others know of this resource and use it. For further information about the RIMS Impaired Physicians Committee call (401) 331-3207.

What of the future? Prevention is our prime objective. Educating physicians regarding addic-

tion is crucial. Teaching ways of dealing with stress and feelings is essential but does not fit readily into the customary medical education process. Furthermore, medical students are selected largely on the basis of their intellectual achievement rather than their capacity to recognize and deal with feelings and human relationships.

In the absence of healthy coping strategies addiction and other self-destructive behaviors may serve as protection against the emotional pain inevitable in life. These patterns are rooted in early development. Prevention of addiction thus would require both education and personal experiences. For medical students these might include close association with faculty members (eg, as preceptors) knowledgeable in the dynamics of human feelings, attendance at AA meetings and the cost-free availability of absolutely confidential counseling services by persons competent in addictions.

For further information call (401) 331-3207.

Doctors in practice are more difficult to approach, being in diverse environments and having varied and well established behavior patterns. The RIMS Impaired Physicians Committee will assist persons at any stage of addiction but seldom encounters early cases. Lack of recognition of the problem and the perception of personal threat by all involved often serve to prevent treatment until the symptoms are so severe that they constitute a danger to the person or others.

It has been said that "A little knowledge is a bad thing." In the case of addiction a little knowledge rather may be a doorway for recognition of the problem and referral for help.

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¹ Webster TG, Problems of Drug Addiction and Alcoholism among Physicians in "The Impaired Physician." Scheiber, SC, Doyle, BB eds. Plenum Books, NY 1983.

² Morse RM, Martin MA, Swenson WM, Niven RG. Prognosis of Physicians Treated for Alcoholism and Drug Dependence. JAMA 1984;261:743-746.

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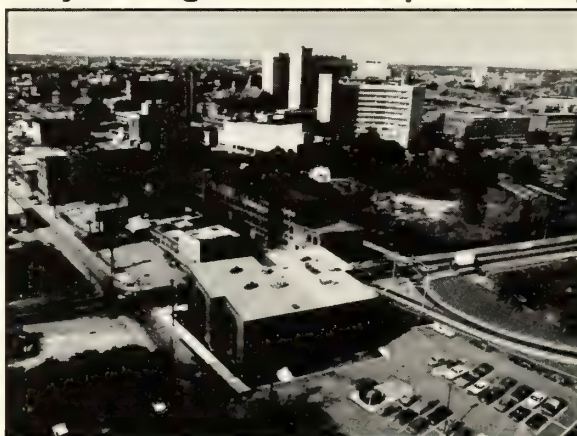
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What Practicing Physicians Need to Know about Self-Help for Chemical Dependents

Bruce E. Donovan, PhD

Alcoholics Anonymous is a suitable treatment for those who have a desire — sometimes first apparent to others as a need — to stop drinking.

Introduction: The Example of Alcoholics Anonymous

Self-help groups, more aptly called mutual-help groups, have been used in treating chemical dependence for over 50 years and seem to grow steadily more popular.¹ The most prominent mutual-help group, Alcoholics Anonymous, has served as the model for many others, including Narcotics Anonymous and anonymous groups dedicated narrowly to other drugs. Although in some ways idiosyncratic, AA well represents the general movement and will be the subject of this discussion.²

Chemical Dependence

Combined Self-Help & Medical Approaches

Some alcoholics never require formal medical care. They approach AA directly and find its program adequate for their recovery. Many others, particularly those who initiate their recovery with in- or out-patient treatment, combine self-help with traditional medical care.

Over the years, individuals both in and out of AA have felt uneasy with this combination of AA and more traditional medical options. The difficulty arises in part from the tension between non-professional self-help and conventional care

offered by a licensed physician. This tension has been aggravated because many alcoholics distrust the medical profession. Many physicians, on the other hand, are reluctant to accept the AMA's definition of alcoholism as a disease — one of AA's basic tenets — and question the correctness of a medical approach.

Increasingly, cooperation has become easier. One reason may be that many medically-based treatment centers across the country now incorporate AA as a staple of treatment. Second, the number of AA members who have profited directly from formal medical care grows steadily. Although the debate continues as to whether alcoholism is an illness, or is better seen as a behavioral problem or as a hybrid of these two concepts, there is increasing recognition that different treatments can play complementary roles.³

Cooperation can be highly effective. AA does not run treatment centers or offer counseling based on more than members' own experience-grounded observations: there is ample room for medical authority and practice. AA supplements such professional initiatives, where necessary, and is particularly helpful to alcoholics over the long haul of recovery: the prospect of free, international, 24-hour-a-day support is a very good bargain indeed.

Bruce E. Donovan, PhD, is Associate Dean for Problems of Chemical Dependency, Associate Dean of The College, and Professor of Classics, Brown University, Providence, Rhode Island. Dr Donovan publishes, lectures and consults nationally on problems of chemical dependency in the collegiate setting.

ABBREVIATIONS USED:

AA: Alcoholics Anonymous
COAs: Children of Alcoholics
NA: Narcotics Anonymous

Supported by society's growing general understanding of addiction, mutual understanding in treatment is increasing too. The general AA view of the medical profession, in fact, has changed markedly during the last decade. At AA meetings in earlier days, when medical training in addiction was even less prominent than now, one frequently heard open hostility and derision aimed at doctors, sometimes the result of misdiagnosis and improper treatment — eg, the loosely supervised prescription of tranquilizers — sometimes the result of addicts' lack of candor in dealing with physicians. Such talk is occasionally heard today. However, even as in the old days, it is important to remember that this tension is not part of AA's credo — "AA is not allied with any sect, denomination, politics, organization or institution; does not wish to engage in any controversy; neither endorses nor opposes any causes" — but represents the view of individual alcoholics speaking from their personal experience.

AA's Purpose: The Preamble

Just what AA is and is not is clear from the Preamble, which is read at the beginning of every AA meeting:

"Alcoholics Anonymous is a fellowship of men and women who share their experience, strength and hope with each other that they may solve their common problem and help others to recover from alcoholism.

The only requirement for membership is a desire to stop drinking. There are no dues or fees for AA membership; we are self-supporting through our own contributions. AA is not allied with any sect, denomination, politics, organization or institution; does not wish to engage in any controversy; neither endorses nor opposes any causes. Our primary purpose is to stay sober and help other alcoholics to achieve sobriety."

The essential character of Alcoholics Anonymous is immediately clear to every visitor to an AA meeting — a commitment to "the shared honesty of mutual vulnerability openly acknowledged" and to recovery from alcoholism for all members.⁴ This is the real stuff of AA — the sharing first-hand of the anguish of active alcoholism suffered by men and women of all ages from all sorts of personal and professional backgrounds, and the strength and hope that result from arrest of the illness. This wisdom and the sense of community that derives from "having

played against the team" gives AA its authority and effectiveness.

The fiercely guarded independence of AA — in matters of principle and finance — and the assertion that the fellowship's "primary purpose is to stay sober and help other alcoholics to achieve sobriety" deserve particular emphasis.

The Newcomer's Approach to AA

"There are no volunteers in the addicts' army." Alcoholics at the end of their drinking road, despite outward contrition, confidence or bravado, know great fear at what life will be like now, without their constant companion, alcohol. As a result, alcoholics on the verge of quitting need the support and assurance that life can be lived — and lived enjoyably — on other terms.

The first AA meeting can be a great source of strength. Here, for the first time for many, the drinker is welcomed warmly by an unquestioning group of people who know pretty clearly what life has been like. Empathy is immediate and instinctive. "Clearing up the wreckage of the past" can wait for another day. For now, acceptance and support are the order.

The anxious newcomer may appreciate being accompanied by an AA veteran, though many go to their first meeting alone. The warmth of the proceedings is striking: eager handshakes, a succession of smiling faces, none of the castigation which has come to be expected or feared from all sides. Newcomers hear the uncomplicated slogans that they will use daily to straighten out their complicated lives: "Keep It Simple," "First Things First," "Think," "Live and Let Live" and "Easy Does It" among others. Sympathetic laughter may fill the room; in this setting, surely, where recovering alcoholics come to reaffirm their determination to never again fall into drinking, the old adage "It hurts too much to cry" has real meaning. Such acceptance and the identification that will follow wordlessly help to combat the stigma that still attaches itself to the alcoholic.

Soon the newcomer will have a new circle of associates. Most seek out an older member as "sponsor," an individual who is willing to take time one-on-one to explain the workings of the Program and discuss intimate aspects of the drinker's story. For some, concerned acquaintances will be something of a novelty; others adopt these new faces as partners in recovery and as social partners also; and some draw a line between the world of social intercourse and the world of mutual-help therapy. For some, the first meeting begins a lifelong affiliation, one that will

at first involve heavy attendance and then a lighter regimen for maintenance as the sober days stretch out. For many former drinkers, continuing involvement with AA provides support with the stresses of everyday living and a growing spirit of contentment.

AA's Program of Recovery: The Twelve Steps

AA newcomers are encouraged "to identify and not compare," to try to recognize familiar elements in the personal histories (the 'drunkalogues') of older members. Many times they identify at the level of motivation or feeling, and not in particular details. For this reason, it is not surprising to hear an older, heavy-drinking roustabout acknowledge elements of his own history in the superficially quite different drunkalogue of a protected housewife of means. This sharing of anxiety, guilt and shame allows for relatively easy and immediate identification among members. The perceptions that one is neither alone nor unique — and that self-perceived helplessness can be overcome — offer initial comfort and encouragement to the addict.

Sharing common experiences erodes the denial of difficulties developed over years of drinking: addicts seem to see more quickly in others those things that fear and desperation kept them from seeing in themselves. This process may begin as soon as an addict confronts another person with similar history. For others, the process of identification and the breakdown of denial may take more time.

Alcoholics on the verge of quitting need the support and assurance that life can be lived — and lived enjoyably — on other terms.

Once addicts recognize the nature of their difficulty and determine that some remedy is necessary, recovery can begin. Recovery will, AA members believe, follow a certain course and involve certain stages recognized by the earliest members of the Fellowship and articulated by them as "The Twelve Steps." Although these Steps are only a suggested road map for recovery — "AA has no 'musts'; take what you want and leave the rest" — most members with lengthy records of recovery find that they have, in fact, "taken the Steps" even though they may not have done so consciously or with set goals. Long-term members recommend that newcomers focus directly on "the Steps" to give their recovery a definite form and procedure.

The Twelve Steps: Roadmap for Recovery

1. We admitted we were powerless over alcohol — that our lives had become unmanageable.
2. Came to believe that a Power greater than ourselves could restore us to sanity.
3. Made a decision to turn our will and our lives over to the care of God as we understood Him.
4. Made a searching and fearless moral inventory of ourselves.
5. Admitted to God, to ourselves and to another human being the exact nature of our wrongs.
6. Were entirely ready to have God remove all these defects of character.
7. Humbly asked Him to remove our shortcomings.
8. Made a list of all persons we had harmed, and became willing to make amends to them all.
9. Made direct amends to such people whenever possible, except when to do so would injure them or others.
10. Continued to take personal inventory and when we were wrong promptly admitted it.
11. Sought through prayer and meditation to improve our conscious contact with God as we understood Him, praying only for knowledge of His will for us and the power to carry that out.
12. Having had a spiritual awakening as the result of these steps, we tried to carry this message to alcoholics, and to practice these principles in all our affairs.

The Steps, in essence, require individuals to recognize their inability to solve their drinking problem on their own and the need to seek some form of outside help. One part of this recognition is the evident conflict between personal values and the facts, as they have developed through drinking, of alcoholics' "unmanageable" everyday lives. Members are urged to review their lives, the good and the bad, and discuss these autobiographical reviews (their "inventories") with another AA individual. They then are encouraged to rid themselves of those "character defects" that have caused difficulties and will continue to cause discomfort (or perhaps a relapse, a "slip" in AA's jargon) if they are not addressed.

Encouragement is also given to "make amends" in word or deed where the drinker has injured others. AA members who follow the Twelve Steps will maintain a daily check on their behavior, trying to live positively and usefully without al-

cohol and to help others achieve this same productive, contented, alcohol-free way of life. Such a life of equanimity and decent purposes will be one indication that the individual is truly "sober," and not merely "dry" or simply "a drunk away from a drink."

A Day at a Time

Members often refer to the "24-hour-a-day" way of life. This formulation emphasizes again the need for the alcoholic to maintain a constant check against drinking and to be on guard against those situations which may trigger a drinking episode. The same thinking allows drinkers to stay away from a drink and to try to live "one day at a time" — rather than facing the unthinkable prospect of a lifetime without alcohol. Better, reasons the AA member, to collect a series of manageable days without drinking than aim immediately for a sober life.

Stumbling on the Steps

Sometimes an individual will have difficulty with the Twelve Steps. Some, for cultural reasons, find the concept of powerlessness alien. Others are troubled by mention of "a power greater than ourselves" and recurring references to "God," even though each reference bears the qualifier "as we understood Him." Others find it objectionable to label themselves "sick" or disturbed, a characterization implicit in the language of the Second Step — "restore us to sanity" — and explicit in other AA publications.

A related concern surrounding "spiritual" elements of AA involves the charge that AA, in relying on the idea of alcoholism as disease, in fact encourages moral laxity since a sick person is not held accountable for misdeeds. Steps Four, Five, Eight and Nine disprove this charge. In fact, AA wisely recognizes that it is crucial to discharge guilt and shame from the past to help the recovering addict face the immediate future with greater equanimity.

Perhaps the reference to God is the greatest difficulty for newcomers to AA, and something that one who makes referrals is well advised to anticipate. This concern that AA is some sort of religious cult or group that fosters a particular orthodoxy may find its origins, apart from concerns that an individual has before coming to AA, in the First Step's reference to the powerlessness of the addict.

The First Step links the idea of an unmanageable life and drinking alcohol. Those who find AA useful discover that unmanageable drinking

has led to a life that is to some extent out of control. Perhaps in this sense only the individual is powerless, ie, is unable to act correctively on the evidence of unhappiness that drinking has caused. Controlled drinking and other measures have failed. Abstinence becomes the only answer. (AA members believe that alcoholics in recovery can never drink in safety: "Once a pickle, you'll never be a cucumber again.") Soon the drinker discovers that drinking is not the only activity that is out of control: the powerlessness originally acknowledged now acquires a broader connotation.

The Second Step asserts that the lost control and power of Step One may be replaced by a "Power greater than ourselves." For some this "power" is the teachings of AA or the group which the newcomer first attends. The definition of "power" is left open, but the need is manifest for the alcoholic to reach out for help, to avoid total self-reliance and wilfulness, the very wilfulness that has so dramatically failed. The central point is that the individual must break out of her or his shell and accept and acknowledge help from an external source.

For some, the "Power greater than ourselves" is the deity of the drinker's religious tradition. For the non-believer who wishes to avoid the notion of "God" the shifting of "power" in the First Step to a proper noun in the Second is difficult. For these individuals the problem is compounded when in Step Three "Power" is replaced by "God." After a period in AA many alcoholics do, in fact, embrace a personal and traditional god. Others, however, for all of their time in AA will choose to use the accumulated lore of AA or the idea of love — anything other than the self — as the source of inspiration and energy that the Second Step mentions.

In discussion of this issue, a priest/member observed that "the nature of God is an interesting question, but it never kept anyone sober." In a rough paraphrase of the preamble, which affirms the intellectual freedom of AA, the alcoholic who does not subscribe to a Judeo-Christian belief is told to "take what you like and leave the rest." Similarly, those troubled by the characterization of God as male are free to characterize God any way they choose. In fact, some members of AA not infrequently invoke a female power or a gender-free creator.

AA's Structure and Organization: The Twelve Traditions

1. Our common welfare should come first; per-

- sonal recovery depends upon AA unity.
2. For our group purpose there is but one ultimate authority — a loving God as He may express Himself in our group conscience. Our leaders are but trusted servants. They do not govern.
 3. The only requirement for AA membership is a desire to stop drinking.
 4. Each group should be autonomous except in matters affecting other groups or AA as a whole.
 5. Each group has but one primary purpose — to carry the message to the alcoholic who still suffers.
 6. An AA group ought never to endorse, finance, or lend the AA name to any related facility or outside enterprise, lest problems of money, property or prestige divert us from our primary purpose.
 7. Every AA group ought to be fully self-supporting, declining outside contributions.
 8. Alcoholics Anonymous should remain forever nonprofessional, but our service centers may employ special workers.
 9. AA, as such, ought never to be organized, but we may create service boards or committees directly responsible to those they serve.
 10. Alcoholics Anonymous has no opinions on outside issues; hence the AA name ought never to be drawn into public controversy.
 11. Our public relations policy is based on attraction, rather than promotion: we need always maintain personal anonymity at the level of press, radio, films and television.
 12. Anonymity is the spiritual foundation of all our Traditions, ever reminding us to place principles above personalities.

As the Twelve Steps constitute AA's program for recovery, the Twelve Traditions clarify the fellowship's principles of purpose and organization. The Traditions state the importance of maintaining AA's independence through financial self-support and of avoiding controversy; of assisting those who seek recovery from alcoholism; of subordinating the interests of any one member to the welfare of the group; and of maintaining personal anonymity.

The principle of anonymity, which provides that members need to know only one another's first names, is essential to the AA process. Tradition Twelve advises members that anonymity, which helps them to consider a message and not the source, helps them "to place principles above personalities." On a more pragmatic level, ano-

nymity allows newcomers to investigate AA without fear of disclosure. And in a world in which stigma and discrimination may haunt the addict, even in recovery, anonymity yields other necessary benefits.

AA Worldwide & in Rhode Island

AA avoids bureaucracy and styles itself, in the language of the Preamble, as a "fellowship." The organization of AA's 1,750,000 members is remarkably simple and democratic. The same principles which pertain locally inform the worldwide network of AA groups. Whenever two or more alcoholics gather together, an AA meeting is in session. In fact, regular meetings are held on a repeating schedule: over forty meetings are held every day in Rhode Island at various hours through the day and night. Those who regularly attend a particular meeting are generally responsible for its affairs: such an association of individuals is known as an AA group.

Groups are self-regulating and operate on the group "conscience" or consensus of Tradition Two. Group members regulate that group's affairs and represent the group at district and statewide meetings of similar representatives from groups around the state. The persons filling these assignments change every six months or so to rotate opportunities for service and to assure that the group does not fall under the direction of any one individual for too long a time.

A member who "chairs" a meeting opens the meeting by reading the preamble and sharing his or her "drunkalogue" — what life was like before AA, how the speaker reached AA and what life has been like since. The chair-person will then follow the agenda established by a particular group. Some meetings will be devoted to discussion of a particular topic. Others will discuss the Twelve Steps, considering each of the Twelve Steps on a rotating weekly schedule. Other meetings have a "speaker" format: each of four or five speakers in the course of 60 or 90 minutes will deliver her or his own "drunkalogue." Meetings close with a prayer, a voluntary collection and light refreshments.

The range of meetings is wide. Some are closed to the general public and open to alcoholics only. Others are open to all who wish to attend and are particularly appropriate for the uncertain or the curious. Most are targeted to the general public, but others have a particular focus: men, women, gays, lesbians, foreign language speakers, young people, the deaf, even professionals such as physicians or lawyers.

Some do not allow smoking; many have wheelchair access. Some will welcome those whose stories include heavy drug use; others prefer a focus more restricted to problems with alcohol. There is very likely a meeting for every need — and for needs unmet a meeting can be started — and a meeting that can fit into almost any schedule: early morning, through the day and on into the late night hours. All are united by the common purposes of AA, and any meeting, whatever its particular focus, is open to all those with a desire to stop drinking. Drinking alcoholics who still hope to stop drinking are also welcome at meetings — “What better place to spend time for an alcoholic who can’t stay stopped?”

How AA Can Help: The Physician’s Referral

Although AA is not the only approach to the treatment of alcoholism, it has helped a wide range of individuals in over 50 years and compiled a strong record of achievement. Should there be indication that a patient may profit from further investigation of possible alcoholism or from the continuing support that AA can provide, referral is in order. AA is glad to receive these individuals and is prepared to cooperate fully.

The most effective referrals will be made by those who know something about how AA works. AA publishes an array of brochures on alcoholism, AA itself, and on special populations, including a pamphlet — among several focused at physicians — entitled, “Alcoholics Anonymous as a Resource for the Medical Profession.” AA also publishes books, the largest and most significant of which is “the Big Book,” *Alcoholics Anonymous*, that describes the fellowship and its operations and includes representative “drunkalogues” of recovering alcoholics. The physician may find illuminating — and useful for display in a waiting room — the pamphlet of twelve diagnostic questions, “Is AA For You?”

Many medically-based treatment centers across the country now incorporate AA as a staple of treatment.

Physicians, along with the general public, are welcome at open meetings. Attendance at a variety of meetings is worthwhile both to observe AA in operation and to help in imagining just how the alcoholic, frightened and alone, may feel at an initial meeting.

Using AA’s Resources

Physicians are urged to establish a liaison with

AA, perhaps utilizing recovering patients, sober for a while, who are happy to accept referrals and serve as guides to newcomers. Members of AA are happy to provide this assistance as a form of service and as part of their own recovery (“Twelfth Step work”). To establish contact and procedures for referrals, physicians who do not know recovering persons may call the General Service Office of AA (number in telephone directory under “AA”); AA’s Committee On Cooperation with the Professional Community will be pleased to help.

In making referrals, the physician’s attitude will be significantly important. If tentative or even slightly derisive, the referral will lack authority and will likely fail. A referral based on some understanding of AA, including possible points of difficulty, that is confident and hopeful and involves support from a recovering member will have a far greater chance of success.

Reaction to a newcomer’s comments on initial contact with AA will also be significant. Some points of awkwardness may be anticipated: the procedures of AA are unique in most people’s experience and require time for familiarity to develop. Some newcomers will find the very thought of involvement with AA anathema. The physician’s supportive questioning and gentle prodding will help the newcomer stay the course and allow appropriate time for a balanced view. If a first meeting is unappealing, for example, the physician may recommend a second in another area or with another format.

Such patient attention may not be easy: some physicians find it taxing to support a system of treatment which is so colloquial, so non-professional, so dependent on the apparent autonomy of the patient and lacking in individual authority, a program which knows no “musts.” Or the physician may want to insist on a long-term commitment to abstinence and grow weary of AA’s quasi-paradoxical insistence that such oaths are foolish, that the drinker is best advised not to drink “a day at a time.” The infusion of spiritual concerns and value questions in recovery may also be novel and a source of strain for both physician and patient. However, if willing to check personal reservations, even while acknowledging individual points of contention, the physician can provide useful service. It is helpful to underscore the potential value of AA and to reject the individual’s suspicion prior to full investigation.

Epilogue: Other Self-Help Groups for Chemical Dependents and Their Significant Others

Alcoholics Anonymous is a suitable treatment for

those who have a desire — sometimes first apparent to others as a need — to stop drinking. This population will surely include individuals with other problems in their lives: the desire or need for therapy regarding drinking is the requisite detail. For those whose drug(s) of choice was other than alcohol, Narcotics Anonymous may be the appropriate referral. Many addicts alternate between these two groups and occasionally utilize more specifically targeted groups as well, eg, Cocaine Anonymous.

Al-Anon and Nar-Anon, and specialized groups for Adult Children of Alcoholics/Addicts (COAs) are available for those who have been affected by the drug use of another. The principles of these fellowships are the same as those found in other "Anonymous" groups. A very common misunderstanding centers on the misconception that Al-Anon, for example, is a group to teach a spouse or significant other how to stop the drinker from drinking. Wrong. Al-Anon is a fellowship which provides support for and guidance to those who are involved with drinkers by providing insight as to how they may live contented lives whether the drinker in question is dry or sober or not.

Finally, a burgeoning array of self-help groups is developing around other issues. The physician may find it helpful to investigate, eg, Gamblers Anonymous, Overeaters Anonymous or Sex and Love Addicts Anonymous, groups that address issues that may be confronted among recovering alcoholics.

For further information on a particular self-help/mutual-help group, consult the white pages of the telephone directory or call Information.

References

- 1 The terminological question is addressed by Phyllis Silverman in the Introduction (p 7) to Madara, E. and Meese, A, eds., *The Self-Help Sourcebook* (Second Edition, 1988), St. Clare's-Riverside Medical Center, Denville, NJ 07834, a full, instructive and periodically updated compendium of self-help organizations for a wide range of issues.
- 2 For other self-help groups for chemical dependence, see Reference 1, above.
- 3 For an illuminating discussion of self-help that shows the extent to which behavioral strategies are, in fact, imbedded in AA processes, see McCrady, B, and Irvin, A, "Chapter 10: Self-Help Groups," pp 153-169, in Hester, RK and Miller, WR, *Handbook of Alcoholism Treatment Approaches: Effective Alternatives*, Pergamon, New York, 1989.
- 4 Kurtz, E, *Not-God: A History of Alcoholics Anonymous*, Hazelden, Center City, Minnesota, 1980, p 214.

NB Unattributed quotations are comments heard at AA meetings and are attributable only to anonymous members and the lively folk tradition of AA.

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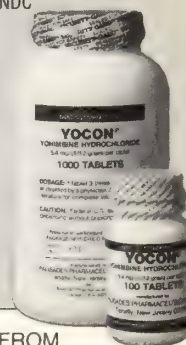
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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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Detoxification of the Chemically Dependent Patient

Alan A. Wartenberg, MD

In patients with a history of severe withdrawal, or when medical or psychiatric conditions make the alcohol withdrawal syndrome more dangerous (such as coronary heart disease, diabetes, hypertension, chronic lung or liver disease, depression or psychosis), an inpatient or residential setting should be considered.

The Chemically Dependent Patient in Medical Practice

An estimated 20 million Americans regularly use beverage alcohol in the United States. There are about 800,000 heroin addicts, with a larger number of occasional and regular abusers of medicinal opiates. Between two and three million Americans take non-prescribed hypnotic sedative drugs regularly. In addition, the use of cocaine and other stimulants is widespread, with at least five million regular users of cocaine in the US.¹ Patients with chemical dependency (CD) are overrepresented in medical practice; while they may comprise 5-8 percent of the adult US population, 15-30 percent of patients in office practice, 30-40 percent of patients in general hospitals, and 50 percent or more of patients in public hospitals may have primary or secondary CD problems.²

Acute or subacute discontinuation of alcohol, hypnotic sedatives, opiates and cocaine is associated with mild to severe syndromes which complicate other medical, surgical or psychiatric conditions, and can result in significant morbidity or mortality. Since the great majority of patients with CD do not fit the standard stereotype of the "drunk" or "junkie," diagnosis is often missed.

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This may result in the development of hyperautonomic states and/or delirium tremens (DTs), seizures, or drug-seeking behavior, failure to follow recommended treatment or leaving the hospital against advice.

It is important for practicing physicians to become familiar with the tools needed for making a CD diagnosis. As in all of medicine, the primary tool is the medical history. A complete list of all psychoactive substances, prescribed or non-prescribed, should be included in all histories. Simple techniques, such as the CAGE questionnaire (Fig 1), or asking whether patients believe they have ever had an alcohol problem and whether they have used alcohol in the last 24 hours,³ may yield a presumptive diagnosis in many patients.

ABBREVIATIONS USED:

AWS: alcohol withdrawal syndrome

BAC: blood alcohol concentration

CAGE: see figure 1

COPD: chronic obstructive pulmonary disease

CD: chemical dependency

DTs: delirium tremens

GGT: gamma-glutamyl-transpeptidase

IM: intramuscular

MCV: mean corpuscular volume

NPO: nothing by mouth

PO: by mouth

Q: every

QID: four times per day

SGPT: serum glutamic pyruvic transaminase

SGOT: serum glutamic-oxaloacetic transaminase

Understanding laboratory markers, such as hyperuricemia, hyperlipidemia, elevated GGT, MCV, SGPT/SGOT (SGOT > SGPT), and the use of blood alcohol concentrations and urine toxicology screens, may aid the physician in the diagnosis.

Alcohol Detoxification

Patients at risk for alcohol withdrawal have usually been drinking daily, generally consuming over 100 grams absolute ethanol per day (one standard drink = 12-14 grams) for at least 7 days. At such levels of consumption, the Alcohol Withdrawal Syndrome (AWS) is usually mild, increasing in severity with increasing amounts of alcohol and duration of use. However, considerable variability occurs in individual alcohol metabolism, body mass, gender, age; concomitant medical conditions, and use of other drugs may also alter the development and severity of AWS.

Patients with a high blood alcohol concentration (over 150 mg percent) who appear only minimally intoxicated are at greater risk of serious AWS, as are those with BAC over 300 mg percent who are conscious and alert. One should not rely on the smell of alcohol on the breath; the BAC should be measured.

Figure 1

THE CAGE QUESTIONNAIRE

- C** — HAVE YOU EVER TRIED TO **C**UT DOWN ON YOUR DRINKING?
- A** — DO YOU GET **A**NGRY OR **A**NNOYED WITH COMMENTS ON YOUR DRINKING?
- G** — DO YOU EVER FEEL **G**UILTY ABOUT YOUR DRINKING?
- E** — DO YOU NEED AN **E**YEOPENER UPON ARISING (A MORNING DRINK)?

Diagnosis

The AWS is initially marked by anxiety, restlessness, insomnia, anorexia, diaphoresis, tachycardia, systolic hypertension, hyperreflexia and tremor (Stage I). In addition, headache, nausea/vomiting and diarrhea may be present. This occurs 6-12 hours after a reduction in the usual blood alcohol concentration, and if uncomplicated will peak at 24-36 hours, resolving within 48-72 hours. In some patients auditory hallucinosis may occur, with preservation of orientation and judgement, usually at 36-72 hours (Stage II). In 5-15 percent of patients grand mal seizures will occur, usually at 12-48 hours into the course (Stage III). They generally involve a single seizure, but a salvo of 2-4 seizures with intervening

consciousness is not infrequent. Status epilepticus is unusual. First seizures should be evaluated as one would any seizure; increased suspicion of an underlying disorder is warranted if seizures are focal, occur more than 72 hours after discontinuance of alcohol, or any neurological abnormality is present.

The most severe form of AWS is delirium tremens (Stage IV). There is marked autonomic hyperactivity, with profuse diaphoresis, tremor and hyperpyrexia, as well as global confusion and florid hallucinations, which may be auditory, visual, tactile or olfactory, and may be fused. Patients who have sustained accidental or surgical trauma and those with severe medical illness (pancreatitis, pneumonia or gastrointestinal hemorrhage) or other severe stresses are at greatest risk of developing DTs. Stage IV AWS generally occurs at 72-96 hours, and may last for several days. Patients who have had a seizure may be at greater risk of developing DTs later in their course.

Hypoglycemia and hypomagnesemia should be sought for and treated if present. General care of fluid, electrolyte and acid-base status is important in more seriously ill patients. A metabolic acidosis is generally secondary to alcoholic ketosis, but methanol and ethylene glycol ingestion should be excluded. All patients should receive adequate thiamine (initially 100 mg by mouth or intramuscularly in debilitated patients) and multivitamin support, including Vitamin C, niacin, folic acid and pyridoxine.

Treatment

A schema for treatment of AWS is outlined in Table 1. In mild cases of Stage I AWS, with no history of prior seizures or DTs and no serious underlying medical or psychiatric problems, treatment may be limited to extensive psychosocial support (social setting detoxification). If the patient has adequate social support, outpatient detoxification may be considered. There should be a responsible relative or friend to provide monitoring and administer medications. One or two days of medication can be provided, with telephone contact urged if the condition worsens. The patient should be seen every one or two days until signs of AWS have abated. In patients with a history of severe withdrawal, or when medical or psychiatric conditions make the AWS more dangerous (such as coronary heart disease, diabetes, hypertension, chronic lung or liver disease, depression or psychosis), an inpatient or residential setting should be considered.

Table 1. Treatment of Alcohol Withdrawal

1. All patients should have adequate medical evaluation for concomitant medical/surgical/psychiatric conditions.
2. All patients should receive thiamine prior to treatment, and continued nutritional and vitamin/mineral support should be considered.
3. Minimal syndrome — Drug-free, reassurance given, adequate but appropriate stimulation, milieu support (social setting detoxification).
4. Mild syndrome — Chlordiazepoxide 10-25 mg po QID for 2-5 days, regular contact with clinician, titrate dosage as needed.
5. Moderate syndrome — Chlordiazepoxide 50-100 mg po initially, then 25 mg Q 3-4h for first 24 hours, then taper total dose by 25-33%/day.
6. Severe syndrome — Chlordiazepoxide 50-100 mg po initially, then 50-100 mg Q 1-2h until adequately sedated, then dc and observe for at least 48h.
7. Emergency management — if very severe, diazepam 5-10 mg IV slow push (2-5 mg/min), may be repeated prn, or Lorazepam 2-5 mg IM or IV may be given and repeated. When stable use po regimen as above.

Cautions:

1. Other benzodiazepines listed in Table 2 may be used in equivalent doses and appropriate intervals. Lorazepam and oxazepam offer advantages in very debilitated patients or those with severe liver disease or COPD.
2. Diazepam and clordiazepoxide are poorly absorbed IM and generally should not be given by that route. Lorazepam is well absorbed IM and lasts 3-4 hours. Initial dose should be a mg or less.
3. Patients must be carefully monitored. Signs of oversedation should lead to withholding doses and decreasing subsequent doses. Continued withdrawal should prompt increased dose or re-evaluation of choice of drug, dosing interval and/or route of administration, presence of hypoglycemia or hypo-magnesemia.

Treatment-Pharmacotherapy

No one drug regimen is clearly superior to others in the treatment of AWS.⁴ Virtually all authorities agree that benzodiazepines are the drugs of choice. Barbiturates (except for phenobarbital), paraldehyde, other barbiturate-like hypnotosedatives, phenothiazines and alcohol offer no significant advantages and are more toxic and difficult to administer, and should generally be avoided. Chlordiazepoxide, diazepam and clorazepate are long-acting, well absorbed and offer a smooth course of action. In mild cases, chlordiazepoxide 25 mg 3-4 times daily for 48 hours, then 10 mg 3-4 times daily for 48 hours is adequate.

In moderate to severe cases, 50-100 mg may

be given initially and repeated every 1-4 hours until symptoms are controlled and a mild state of sedation achieved; the required dose (usually 200-400 mg in 24 hours) may then be given in divided doses and reduced by 25-33 percent per day, observing for signs of oversedation or re-emergence of withdrawal signs. The equivalent doses of other hypnotosedatives may be used, with care to give at appropriate intervals (Table 2). Chlordiazepoxide or diazepam offer significant advantages of smooth and rapid absorption, long duration of action and gradual decline in blood levels, as well as low cost. In patients with severe lung or liver disease (carbon dioxide retention or decompensated cirrhosis), shorter acting drugs (lorazepam and oxazepam) may be safer.

Barbiturates, barbiturate-like hypnotosedatives, and benzodiazepines are similar to alcohol in their mood-altering effect, and may be subject to abuse.

In general, drugs should be given by mouth. Chlordiazepoxide is not well absorbed intramuscularly, and that route should be avoided. Diazepam absorption is predictable only from deltoid sites, but injection is painful. If parenteral drug or rapid induction is required, diazepam 5 mg IV can be given (over 2 minutes) every 15-30 minutes until control is achieved. Lorazepam (Ativan®) is very well absorbed intramuscularly, and lasts for 3-5 hours; an initial dose of 0.5-1 mg should be given, and then incremental doses of up to 5 mg can be given (dependent upon clinical response). Lorazepam can also be given IV with a longer duration of action than diazepam. Repeated doses of IV diazepam may result in late over-sedation. If the patient progresses despite treatment, complicating factors or an alternative diagnosis should be sought, and the drug choice, dosage and route of administration reevaluated.⁵

Beta-blockers may be used to control tachycardia and elevated pressure in the presence of underlying coronary heart disease or hypertension, but should not replace appropriate use of benzodiazepines. The clinician should be especially cautious in giving hypnotosedatives to patients still under the influence of alcohol. BAC concentration should be measured prior to treatment (breath analysis is an acceptable method); inappropriate use of sedatives in an over-sedated and combative patient may result in "paradoxical" excitation, or in respiratory depression with

Table 2 — Hypnosedative Drugs

Generic Name	Trade Name	Half-Life	Equivalent Dose
Phenobarbital	Luminal	24-140 h	30 mg
Pentobarbital	Nembutal	15-48 h	100 mg
Secobarbital	Seconal	19-34	100 mg
Butalbital	Butisol	34-42 h	60 mg
Meprobamate	Miltown	6-17 h	400 mg
	Equanil		
Ethchlorvinol	Placidyl	10-25 h	350 mg
Glutethimide	Doriden	5-22 h	250 mg
Methypylon	Noludar	4-15 h	100 mg
Chloral Hydrate	Noctec	4-10 h	500 mg
Alprazolam	Xanax	12-15 h	0.5 mg
Chlordiazepoxide	Librium	10-24 h	10 mg
Clorazepate	Tranxene	30-200 h	7.5 mg
Diazepam	Valium	26-55 h	5 mg
Flurazepam	Dalmane	23-100 h	15 mg
Lorazepam	Ativan	10-20 h	1 mg
Oxazepam	Serax	515 h	15 mg
Temazepam	Restoril	10 h	15 mg
Triazolam	Halcion	2-4 h	0.5 mg

its attendant complications. In addition, a blood sugar is desirable since hypoglycemia may both mimic and complicate the AWS.

If delirium is present and does not respond to benzodiazepines, haloperidol or droperidol may be used in usual doses for acute psychoses. If the patient is confused or hallucinating, but not agitated, treatment need not be given. Hypomagnesemia may cause tremor, lowered seizure threshold and ventricular irritability; levels should be obtained in seriously ill patients, and consideration given to routine replacement. Oral magnesium supplements are available which are well tolerated (Mag Plus®, Slow Mag®); parenteral replacement may be necessary in debilitated patients or with symptomatic hypomagnesemia.

Hypnosedative Detoxification

Barbiturates, barbiturate-like hypnosedatives, and benzodiazepines are similar to alcohol in their mood-altering effects. The rapidly acting highly lipophilic drugs have the most mood-altering effect, and are highly subject to abuse. These include secobarbital, pentobarbital, ethchlorvinyl, glutethimide, methaqualone, diazepam, lorazepam and alprazolam. However, all of these drugs may be abused, particularly in those who may not be able to obtain their drug of choice. The most commonly used of these drugs, and their equivalent potencies and half-lives are given in Table 2.

The initial treatment of hypnosedative abuse requires detoxification. The abstinence syndrome is similar to that of alcohol, but onset,

duration and severity vary considerably. The shorter half-life drugs are most likely to produce seizures and delirium. While longer half-life compounds produce less withdrawal, in some individuals where metabolism of these drugs may be accelerated (those with significant tolerance, who are drinking large amount of alcohol, or using drugs such as phenytoin), significant withdrawal syndromes can develop after discontinuance or dose reduction of long-acting hypnosedatives.

Patients who are on prescribed hypnosedatives for more than two weeks should in general be tapered off the drug over 5-10 days. In older individuals, the shorter-acting drugs in higher doses are more likely to cause significant abstinence symptoms. Such patients may require longer periods of tapering. Alprazolam, for example, if given in doses of 2-4 mg/day, should be tapered over a 4-8 week period. An individual taking 4 mg daily should have the dose reduced by 0.5 mg week and should be carefully monitored. Some patients may be able to tolerate more rapid tapering, but close observation for autonomic hyperactivity and markedly increased anxiety is required. In some cases, it is difficult to differentiate the return of pre-existing anxiety from the abstinence syndrome, but the latter is often associated with light-headedness and paresthesias.⁷

In hypnosedative abusers, sudden discontinuance may lead to status epilepticus and delirium tremens. Tolerance can be determined using the pentobarbital method of Wesson and Smith.⁸ Pentobarbital 200 mg by mouth is given initially; if after one hour no signs of toxicity appear (sedation, sustained nystagmus, dysarthria, ataxia or lability of mood), an additional 100 mg is given hourly, until either the point of toxicity or 800 mg total is reached. The total required dose is then converted into phenobarbital (100 mg Pentobarbital = 30 mg phenobarbital) and that amount is given in divided doses three or four times a day, tapering by 5-20 percent per day. It may be preferable to give the first 24 hours of phenobarbital intramuscularly, since oral absorption is slow, and it should be given no sooner than four hours after the last pentobarbital dose, and/or when the patient is not clinically intoxicated.

Opiate Detoxification

Opiate abstinence is characterized by intense drug craving, myalgias, abdominal and back pain, nausea, vomiting and diarrhea. Mild to moderate autonomic hyperactivity is seen, with tachycardia, tremor and diaphoresis. In addition, laci-

mation, rhinorrhea, mydriasis and piloerection occur; the latter phenomenon gives rise to the term "cold turkey" for sudden cessation of opiate use, since "gooseflesh" is common. Seizures and delirium are not part of the syndrome; if present, an alternative or concurrent condition should be suspected. Abstinence syndromes from street heroin vary according to drug purity. Currently in Rhode Island, very pure heroin is present on the street. An average "bag" of heroin contains up to 10 mg of heroin, with lactose, quinine or other powders as filler. An average habit may be one "bundle" or 10 bags, containing up to 100 mg of heroin, and costing \$200 or more daily.

Withdrawal may be carried out with methadone for abusers of most opiates; propoxyphene, pentazocine and codeine also may be used in tapering doses for abusers of those drugs. Methadone 5-10 mg is given by mouth, and may be repeated after 3-4 hours, titrating to removal of objective signs of withdrawal. In general, methadone is inappropriate unless clear signs of withdrawal (particularly mydriasis and piloerection) are present, or if the patient is known to be using high doses of medicinal opiates or methadone that can be verified. Most patients on short-acting opiates can be controlled with 20-40 mg methadone daily. This can then be given in a single morning or evening dose, and the dose tapered by about 20 percent of the original total dose per day. Patients who are not already on a methadone maintenance program cannot legally be maintained on methadone and must be detoxified.

In patients who are NPO, two-thirds of the usual methadone dose may be given intramuscularly in 2-4 divided doses. Care should be taken not to give Naloxone since it will precipitate severe withdrawal. Mixed agonist-antagonist drugs such as pentazocine may also cause withdrawal. If such a reaction occurs, clonidine may be used to ameliorate symptoms.

Opiate addicts may present extremely manipulative and drug-seeking behavior. Clinicians with skills and experience with addiction should be consulted. Patients may present multiple subjective symptoms of withdrawal without any concomitant objective signs. The detoxification should proceed as scheduled unless clear-cut and severe re-emergence of objective withdrawal signs occur. If required, clonidine may be used to supplement the methadone withdrawal (see below). Frequent urine toxicology screens should be obtained to look for surreptitious use of drugs in hospital; the act of voiding should be observed by staff, or it should be done in a setting which

precludes exchange of urine. The patients should be told upon admission that these screens will be done, and what the consequence will be for drug use in hospital (discharge, restriction to room, no visitors, etc).

Withdrawal may be carried out with methadone for abusers of most opiates; propoxyphene, pentazocine, and codeine may be used in tapering doses for abusers of these drugs.

Opiate withdrawal symptoms may be significantly mitigated with clonidine, an alpha-2 agonist, which reduces the autonomic and vasomotor signs, and to some extent ameliorates craving.⁹ For low-dose opiate habits, or for those on low doses of methadone (30 mg or less), clonidine may be successful as the sole agent used in withdrawal. A single 0.1 mg dose may be given by mouth if the blood pressure is greater than 100 systolic, and then may be repeated every 1-3 hours, keeping the systolic pressure over 90 mm. Alternately, 0.1 mg may be given four times a day the first day, then increased to 0.2 mg QID the second day, 0.3 mg QID on day 3, with 0.1 mg doses available on a prn basis, holding for lower systolic pressures. Once the patient has stabilized, the dose should be decreased by 0.1 mg per day until it is discontinued. A limiting feature is the development of significant hypotension; if this occurs, the patient should be placed in Trendelenberg position, and fluids may be required. Pressors are rarely needed.

In patients undergoing methadone detoxification, smaller supplemental doses of clonidine (0.1 mg every 3-4 hours) may be used, but hypotension may be more frequent. Patients who are on very high doses of heroin, or those on 40 mg or more of methadone, generally do not tolerate clonidine detoxification well. Expert consultation should be sought from those with experience in opiate detoxification. Most patients, regardless of method of detoxification, will experience significant symptoms, which may last for several weeks or longer. Reassurance as to ultimate improvement should be given, and efforts made to use non-pharmacological techniques, such as relaxation therapy, biofeedback, exercise and a supportive milieu. Severe muscle pain may be treated with non-steroidal antiinflammatory drugs, cramps and diarrhea with antispasmodics, and insomnia with the short-term

and judicious use of hypnosedatives. L-tryptophan has been used but recent reports of eosinophilia have led to its withdrawal.

Newer Techniques in Detoxification

The use of loading doses of benzodiazepines has been studied extensively, and appears to be a safe and effective way of managing the AWS.^{10, 11} In this technique, chlordiazepoxide 50-100 mg, diazepam 10-20 mg or equivalent dose of long-acting benzodiazepine is given by mouth every hour to a patient in withdrawal until they reach the earliest end-point of toxicity (see hypnosedative detoxification above). The dose required to reach the endpoint should reflect the level of tolerance of the individual, and thus should be an individual titration. The long half-life of the benzodiazepine then provides an "auto-taper." No further drug is usually needed after the initial loading; 3-6 doses are generally required. Disadvantages include potential oversedation, especially in those with lung and liver disease, and the potential reemergence of withdrawal in those who metabolize the drug unusually rapidly. The advantages are rapid return to a sense of well-being, shorter hospital stay, and less drug-seeking.

Carbamazepine (Tegretol®) is being increasingly used for both alcohol and hypnosedative withdrawal.^{12, 13} While initial reports appear promising, further study with larger numbers of patients are needed, as well as clarification of dosage and duration of treatment. If effective, it may simplify the relatively cumbersome current methods of hypnosedative withdrawal, which often require several weeks of treatment, increase inpatient expenses or necessitate giving potentially abusable drugs to drug abusers as outpatients.

A number of methods for reducing the time required for opiate withdrawal, particularly from larger doses of methadone, have been developed, but require considerable staff expertise in techniques. These include using either parenteral naloxone or oral naltrexone to precipitate withdrawal, then giving high doses of clonidine to treat the withdrawal symptoms.¹⁴ This results in an opiate "washout," with an overall shorter duration of dysphoric symptoms, although they are more intense in the short run. High dose benzodiazepine therapy has also been proposed for opiate withdrawal.¹⁵ The above techniques should not be considered the current standard of care; their use should be limited to those with specific skills with detoxification.

Conclusions

Chemical dependency is widespread both in society and in patients presenting with medical problems. Physicians need to develop skills in the detoxification of these patients. Patients may present with multiple drug withdrawal syndromes. It is not uncommon for patients to be using alcohol, benzodiazepines and cocaine, or heroin and cocaine ("speedballing"), or any combination of drugs. The clinical picture can be confusing, but the general principles of treatment remain the same. In cases where there is doubt as to diagnosis or appropriate management, expert consultation should be sought. It is also important for physicians to make referrals to the social work and/or psychiatric service to assist in referring patients into treatment programs.

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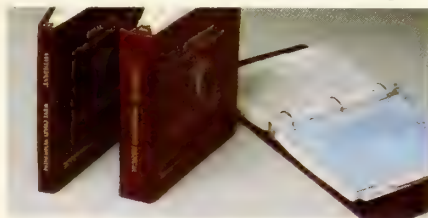
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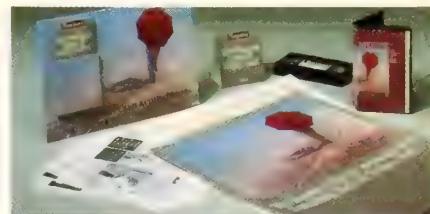
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The Community Gatekeeper Training Model for Reducing Alcohol Abuse and Alcohol-Related Injury

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The use and abuse of alcohol has been identified as the single most important human factor associated with fatal injuries.

Alcohol-Related Injury

Injury is the fourth leading cause of death in the United States, and the leading cause of "years of productive life lost." Injury, in this context, includes both intentional events such as homicide, suicide or injuries due to assault; and unintentional events such as motor vehicle crashes and falls. Among young adults, injury is the leading cause of mortality.¹

Injuries are not random events. Even unintentional injuries are rarely purely "accidental," that

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is, without cause or predisposing conditions. On the contrary, the epidemiology of injury (ie, the scientific study of the incidence, etiology, and prevention of injury) identifies specific factors associated with elevated risk for these events.

The use and abuse of alcohol has been identified as the single most important human factor associated with fatal injuries.² Alcohol consumption is associated with 20 percent of motor vehicle crashes resulting in severe injury, and 50 percent of crashes resulting in fatal injury.³ Use of alcohol is implicated in a large proportion of homicides, rapes, assaults and robberies.⁴

Injury is the fourth leading cause of death in Rhode Island. Motor vehicle crashes and homicides accounted for 42 percent of all injury deaths in the state in 1986. The 1980 Health Interview Survey, sponsored by The Rhode Island Department of Health, found that 71 percent of Rhode Island residents over age 17 consume alcohol, and 8 percent of those who drink are considered to have an alcohol problem. When compared with other states (1978), Rhode Island ranked 12th in per capita consumption of legal alcoholic beverages. A 1983 report by the Rhode Island Department of Health found heavy in-

ABBREVIATIONS USED:

DWI: driving while intoxicated

NHTSA: National Highway Traffic Safety Administration

SAIVE: Stop Alcohol-Related Injury Through Voluntary Effort

volvement of alcohol in both home injury and traffic-related deaths, and estimated total direct and indirect costs of alcohol abuse in the state, in 1979 dollars, at \$283.5 million.⁵

The Alcohol Abuse/Injury Prevention Project

In 1984, the Rhode Island Department of Health received funding, under a Cooperative Agreement with the US Centers for Disease Control and the National Institute on Alcohol Abuse and Alcoholism, to develop and test an innovative approach to reducing alcohol-related injuries in a community.⁶

Traditional strategies to reduce alcohol abuse have focused on public education efforts, increased regulation and enforcement, and other programs directed specifically to problem drinkers. Their primary objective has been to influence the drinker to avoid excessive drinking and its adverse behavioral sequelae, such as drunken driving or domestic violence.

The effectiveness of programs targeted solely to drinkers is limited, however, by: (1) the addictive nature of alcohol, (2) the loss of judgment and control associated with alcohol dependence, and (3) the willingness of "gatekeepers" — family members, alcoholic beverage servers, police — to make excuses for problem drinking rather than intervening to help control the problem.

Gatekeepers as Enablers

Whitfield argues that the family is a system which seeks to protect its integrity and ensure its continuance through adaptation to stressful events and changing conditions. In alcoholic families, this often means that other members of the family, or "codependents," adapt to the family malfunction and to the alcoholic's disease, getting "sick" themselves in the process. This assuming of responsibility for the alcoholic's behavior "enables" the alcoholic to continue drinking.⁷

Reynolds has observed that this same enabling behavior occurs in the community,⁸ for example, when alcoholic beverage servers give an intoxicated person "just one more drink," or when peers view extreme alcohol consumption as appropriate behavior. It also occurs when police fail to charge an injured motor vehicle crash victim with drunken driving because he or she has "already suffered enough," or when an emergency room physician fails to record the role of alcohol involvement in the injury event in the medical record. The project adapted enabling theory to the community in devising its intervention strategy.

The intervention strategy in this community

gatekeeper training model differs from traditional approaches in two ways. First, it is directed at changing the knowledge, attitudes and enabling behaviors, not of problem drinkers, but of gatekeepers in their occupational roles as regulators of community drinking practice. Two groups of gatekeepers are servers (ie, people who sell or serve alcoholic beverages in licensed liquor establishments) and law enforcement officers. The reasoning is that servers and police officers are at the "front line" of alcohol-related injury prevention due to their legally-defined responsibility to control intoxication and driving while intoxicated.

The intervention strategy in this community gatekeeper training model differs from traditional approaches . . . it is directed at changing the knowledge, attitudes and enabling behaviors, not of problem drinkers, but of gatekeepers in their occupational roles as regulators of community drinking practice.

Second, the intervention is to be implemented at the community level, on the assumption that drinking is largely a local social activity. Through the project, a Community Coordinator was located in the one demonstration community to: (1) mobilize community support, (2) secure the cooperation of community leaders, servers, police officers, and others, and (3) help train gatekeepers to understand, accept, and practice "disabling" responses to intoxication and problem drinking by bar patrons, motor vehicle operators, hospital patients, and others.

Project Organization

The initial 18 months of the project were devoted to: research; planning and development activities; staffing; baseline data collection and analyses; selection of one demonstration community and two matched control communities; and securing community involvement.

1. *Staffing.* The project was divided into two components — a research evaluation component and an intervention program component. Twelve full and part-time staff members were employed in the project under the direction of the project director. An expert Advisory Committee was established, which was critical to the success of the project.

2. *Baseline Research.* Three Rhode Island communities were selected for the project, based on

size, incidence of alcohol-related health problems, socio-demographic characteristics, and community resources. For purposes of matching, baseline data were collected for the three Rhode Island cities and towns, including socio-demographic characteristics of the population, vital statistics, hospital discharge data, and police statistics on motor vehicle crashes and arrests. The goal was to collect similar baseline and followup data for three communities to track secular trends in outcome variables and to properly attribute intervention effects.

3. *Selecting Demonstration and Control Communities.* The demonstration community, Woonsocket, was selected at random; the control communities were Newport and Westerly. Continuous hospital and police records abstraction procedures were developed and instituted in all three communities to provide data for evaluating the success of the intervention program in reducing morbidity and mortality resulting from alcohol-related injuries.

4. *Community Involvement.* At project inception, the project director and principal investigator met with civic and political leaders, local media, police and hospital personnel, and alcohol treatment specialists in the three communities to talk about project goals and to get their cooperation with data collection. When Woonsocket was chosen as the intervention site, 1½ years into the project, the project's community coordinator was welcomed by the Woonsocket civic leadership, whose cooperation made a vital contribution to project success. The community coordinator was invited to participate as a member of the Woonsocket Mayor's Task Force on Drug and Alcohol Abuse, and was provided with office space in City Hall for the project's local headquarters.

Choice of Interventions

After reviewing relevant prevention literature, project staff selected three main intervention modalities consistent with the theoretical model of fostering "disabling" behaviors among community gatekeepers: (1) training in responsible service of alcoholic beverages, (2) increased and improved liquor law enforcement, and (3) community mobilization. With involved Woonsocket community leaders, the intervention aspect of the project was given its own name — Woonsocket Says Stop Alcohol-Related Injury through Voluntary Effort (SAIVE).

1. *Responsible Alcohol Service/Training.* The first intervention effort was designed to secure the cooperation of owners and managers of package stores, bars, restaurants and private clubs in

Woonsocket in a training program to increase responsible alcohol service. Owners and managers of liquor establishments were asked to adopt a written policy statement endorsing principles of responsible alcohol service based on Rhode Island dram shops laws (ie, that alcoholic beverages not be sold or served to minors or to visibly intoxicated adults). Owners and managers were then asked to have their sales and service personnel participate in a training program, which had been developed and tested by the National Highway Traffic Safety Administration (NHTSA). This program taught servers techniques for identifying minors and intoxicated patrons, and for denying, slowing down, or cutting off service. The training program also informed them of their legal liability if they failed to obey dram shop laws and taught them ways to protect customers' safety.

2. *More Intensive and Visible Law Enforcement.* The second intervention was to secure the cooperation of the Chief of Police and other law enforcement personnel in Woonsocket to participate in programs to increase arrest rates for DWI and other liquor law violations, and to reduce levels of drunken driving. Police officers were trained (again using NHTSA materials) to recognize intoxication in drivers, to operate breathalyzer equipment, and to conduct sobriety checkpoints. They were also trained to record alcohol involvement on special project forms to improve reporting of alcohol in traffic violations, assaults, and related non-DWI arrests. The police officers were encouraged to increase radar patrols, sobriety checkpoints, and selective enforcement visits to liquor establishments.

The goal of alcoholic beverage licensee interventions was to enforce dram shop laws and local ordinances; for example, reduce sales or service of alcoholic beverages to minors and visibly intoxicated adults.

3. *Community Mobilization and Publicity.* The third intervention was to mobilize the influence of civic and political leaders behind the program, and to encourage broad media coverage of project activities. The purpose was to gain credibility and support for the project, to encourage gatekeepers to participate in the project, and to educate the public in the dangers involved in drinking in high injury risk situations.

Alcoholic Beverage Licensee Interventions

The goal of alcoholic beverage licensee interven-

tions was to enforce dram shop laws and local ordinances, for example, reduce sales or service of alcoholic beverages to minors and visibly intoxicated adults. The sites for intervention were Woonsocket's 17 off-premise establishments (package stores) and 80 on-premise establishments (bars, restaurants, private clubs).

Training programs were established by the Community Coordinator and local server trainers using videotape and other materials developed by NHTSA, supplemented by educational modules produced by the project, such as a 20-minute videotape featuring the Rhode Island Liquor Control Administrator explaining Rhode Island liquor laws. The Community Coordinator met owners and managers in person to secure their participation. Informal leaders of the local alcoholic beverage licensee community were involved in promoting the program among their peers, and two were recruited as SAIVE trainers.

The Mayor's Task Force on Drug and Alcohol Abuse passed a resolution supporting the SAIVE server training program, and participated in the project in an advisory capacity. The City Council passed an ordinance reducing penalties for local liquor ordinance violations for establishments which had adopted the SAIVE policy statement and trained their personnel. Local media provided extensive publicity.

Of pivotal importance to the project was the existence of the Rhode Island Liquor Liability Act, which makes owners, managers, and servers liable for damages caused by illegally served patrons. This was exemplified midway through the project when a 20-year old drunk driver died in a single-car motor vehicle crash after being served in a Woonsocket bar. As a consequence of this event, a 7-day license suspension and a fine were levied against the establishment, and the victim's mother brought a \$2 million suit for civil damages. Reaction in the server and licensee community was immediate and intense, and contributed to the success of the server training program.

Law Enforcement Interventions

The goal of the SAIVE law enforcement intervention program was to substantially (and measurably) increase enforcement of laws against: (1) driving while intoxicated, and (2) selling or serving alcoholic beverages to minors or visibly intoxicated adults.

Through the commitment and with the assistance of the police planning group, particularly the Operations Officer and the Training Officer, Woonsocket officers were trained by project staff and police experts in recognizing intoxicated be-

havior, objectively measuring levels of intoxication, and their legal liability in dealing with intoxicated citizens. The Community Coordinator and the Project Director trained officers to record alcohol involvement on special project forms.

All members of the Woonsocket police force had received training in recognizing and measuring intoxication, the role of alcohol in police work, police liability in dealing with intoxicated citizens, and on-scene investigation of motor vehicle crashes.

The project provided information, equipment, and technical support for increased: (1) radar patrols for speeding and assessment of alcohol involvement, (2) roadblocks used as "sobriety checkpoints," which were funded by NHTSA through the Rhode Island Governor's Office on Highway Safety, and (3) selective enforcement patrols (ie, random spot checks of alcoholic beverage establishments by plain clothes detectives to identify illegal sales or service of alcoholic beverages). Intensive local media coverage was given to law enforcement activities and contributed to their deterrent effect.

Post-Project Evaluation

By the end of the demonstration project, after 18 months of baseline study and 30 months of intervention, the following objectives were achieved:

- 100 percent of off-premise establishments and 79 percent of on-premise establishments had adopted written policies for responsible alcohol service.
- 388 sales and service personnel had been trained in the techniques for responsible alcohol service. This represents nearly 61 percent of servers estimated to be employed in the community.
- All members of the Woonsocket police force had received training in recognizing and measuring intoxication, the role of alcohol in police work, police liability in dealing with intoxicated citizens, and on-scene investigation of motor vehicle crashes.
- The police department had initiated 73 sobriety checkpoints, 47 additional radar patrols, and 11 selective enforcement patrols covering 300 visits to liquor establishments.

Numerous process measures indicate success in community mobilization to secure cooperation of gatekeepers, civic and political leaders, and

the media. For example, the Mayor's Task Force on Drug and Alcohol Abuse has allocated \$6,500 to hire trainers to continue server training and to provide funding to the local police department to conduct selective enforcement patrols in Woonsocket.

The project had a substantial impact on the community, in that staff were able to implement a program that the community supported and chooses to continue on its own. As well, gatekeepers, media sources, and community leaders have been found, through this project, to be committed supporters of the continuing effort to promote responsible drinking and to reduce injury.

The project had a substantial impact on the community.

Baseline and followup surveys of alcoholic beverage servers show an increase in knowledge about alcohol-related injury, and improved attitudes and behavior with regard to "disenabling" illegal or problem drinkers. Also, police department efforts in enforcing DWI liquor law and local ordinances were increased as a result of this project. The Department of Health, through the Community Alcohol Abuse/Injury Prevention Project, is currently evaluating the impact of the project on injury mortality and morbidity rates in Woonsocket, over time and as compared with the control communities.

Conclusion

On the whole, the community gatekeeper training model appears to be a feasible and effective method for reducing alcohol abuse and alcohol-related injury in a community setting. This suggests that the model, along with public education and programs targeted specifically to problem drinkers, should be implemented as a standard part of a comprehensive alcohol abuse and injury prevention program statewide.

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Acknowledgement

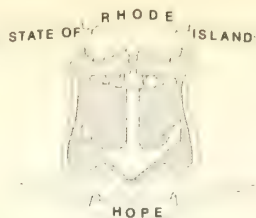
The authors wish to acknowledge the support and assistance provided by the Federal Government, the City of Woonsocket and the project staff. In particular the authors wish to express their appreciation to the two community coordinators, Ann Thacher-Renshaw, MS and Violet C. Morin, EdM, and the project research analyst, Mary C. Speare, MA.

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HEALTH BY NUMBERS

Rhode Island
Department of Health
H. Denman Scott, MD, MPH
Director of Health

Adolescent Substance Abuse Survey: Statewide Findings for 1988

Today in Rhode Island, deaths among children and adolescents are relatively rare and the majority of these cases are injury-related (in 1987, injuries accounted for 75 percent of deaths for Rhode Islanders ages 10 through 19). Among teenagers many of these injury-related deaths can be linked to some form of substance abuse, hence they are preventable.

During 1988, the Rhode Island Department of Health designed and implemented a substance abuse survey (ie, on tobacco, alcohol, and drugs) among adolescents. The study contains responses from 26.6 percent of Rhode Island's public-school students in grades 7 through 12 (n = 15,013).

The data reveal a pattern of substance abuse, epidemic in scope, that begins in elementary school and increases throughout the high school years. A clear example of the pervasiveness of alcohol abuse can be seen in Figure 1 which shows the percent of adolescents who admitted recently getting drunk. Among 7th graders, 10 percent said they were drunk at least once during the previous month. This rate increased to over 49 percent for seniors.

Further evidence of the pervasiveness of substance abuse among teenagers can be seen in Figure 2. Thirty-two percent of 12th graders acknowledged some illegal drug used during the previous month. Crack/cocaine was taken by about 16 percent of these adolescents.

Cigarette smoking is another serious health risk prevalent among adolescents, one whose negative effects will generally not be evident for many years. Figure 3 shows that 35 percent of the 12th grade girls smoke. This is especially noteworthy given that only 24 percent of adult Rhode Island women use cigarettes.

Risk taking among adolescents has a serious impact on our highway safety. More than half of the 12th graders (52 percent) said that they had, at least once, ridden with a driver who was impaired by alcohol and/or drugs.

For further details on adolescent substance abuse in Rhode Island, please refer to: Adolescent Substance Abuse Survey: Statewide Findings 1988. Office of Health Promotion, Rhode Island Department of Health.

Figure 1. Percent of Adolescents who "Got Drunk" During One Month, Rhode Island 1988.

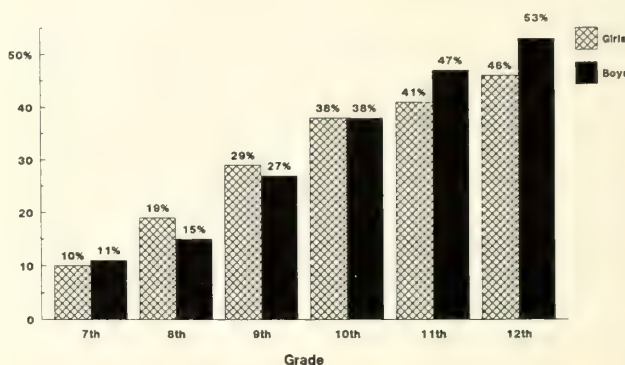


Figure 2. Other Health Risks of 7th and 12th Graders, Rhode Island 1988.

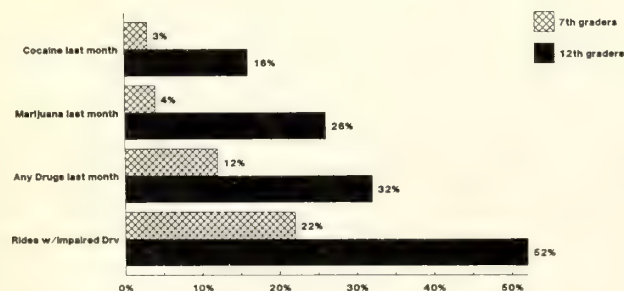
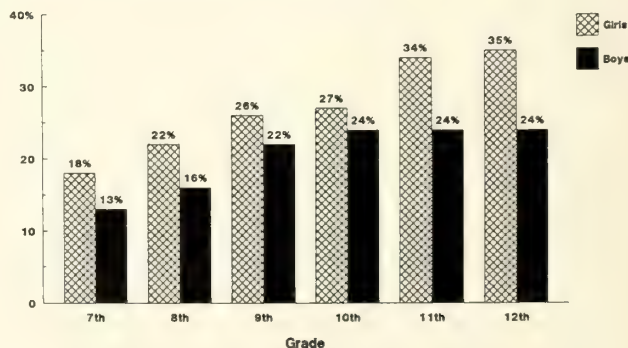


Figure 3. Percent of Adolescents Smoking Cigarettes, Rhode Island 1988.



Submitted by the Office of Health Promotion, Robert J. Marshall Jr PhD, Chief. **Health By Numbers** is edited by Jay S. Buechner, PhD, and William J. Waters, Jr, PhD.

Monthly Vital Statistics Report

Provisional Occurrence Data From the Division of Vital Records

H. Denman Scott, MD, MPH
Director of Health

Roberta A. Chevoya
State Registrar

Vital Events	Reporting Period	12 Months Ending with July 1989	
	July 1989 Number	Number	Rates
Live Births	1,392	14,953	15.1*
Deaths	707	9,688	9.8*
Infant deaths	(20)	(143)	9.6†
Neonatal deaths	(16)	(109)	7.3†
Marriages	803	8,341	8.4*
Divorces	248	3,755	3.8*
Induced Terminations	667	8,005	535.3†
Spontaneous Fetal Deaths	97	1,132	75.7†
Under 20 weeks' gestation	(90)	(997)	66.7†
20 + weeks' gestation	(7)	(114)	7.6†

*Rates per 1,000 estimated population.

†Rates per 1,000 live births.

Underlying Cause of Death Category	Reporting Period	12 Months Ending with April 1989		
	April 1989 Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	290	3,580	360.5	5,100.5
Malignant Neoplasms	183	2,425	244.2	7,749.5
Cerebrovascular Diseases	45	615	61.9	994.0
Injuries (Accident, Suicide, Homicide)	39	434	43.7	9,659.0
COPD	26	316	31.8	444.5

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 current estimated population of 993,000.

(c) Years of Potential Life Lost (YPLL)

NOTE: Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

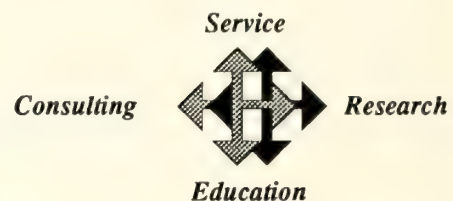
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THE RHODE ISLAND MEDICAL JOURNAL

The Official Organ of the Rhode Island Medical Society
Issued Monthly under the direction of the Publication Committee

VOLUME I
NUMBER 1

PROVIDENCE, R. I., JANUARY, 1917

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THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

Fifty Years Ago (December, 1939)

The lead article, entitled "Anorexia Nervosa" and written by George H. Alexander, MD of Butler Hospital, provides the reader with a careful analysis of the psychological components which may underlie this disorder. The author presents a detailed case history: "A fifteen-year-old girl who had progressively decreased her food intake in order to lose weight, was admitted to the hospital about ten months after starting to diet. Her weight had fallen from 130 to 73 pounds and there was extreme emaciation, hypotension, bradycardia, very low basal metabolic rate, and suppressed menses. Mild personality disturbances were present. Treatment for five months by restricted physical activity, high caloric, high vitamin diet, intensive hormone injection and psychotherapy produced no significant improvement, physically or mentally. All endocrine therapy was then abruptly omitted and treatment continued only by the use of diet and psychotherapy. The response was immediate, favorable, and progressive. Within four months the patient has attained a weight of 116 pounds and was physically and mentally improved to the extent that discharge from the hospital was possible. This sudden and dramatic shift toward recovery was simultaneous with the discontinuance of all endocrine therapy and with a favorable change in emotional fields during the course of psychotherapy.

"The psychotherapeutic approach revealed the true reason for the patient's dieting and the subsequent development of her anorexia nervosa. The decisive dynamic factor lay in the anxiety created by a pregnancy fantasy. With psychotherapeutic treatment, the patient was enabled to master her underlying emotional conflict, and to eat adequately again. On discharge nine months after admission, physical and mental health was normal except for the persistence of amenorrhea."

The lead editorial, this being December, warns the practicing physician that this is the season for respiratory tract infection. Of the many respiratory infections, the editorial notes, the most important is pneumococcus pneumonia. "Although the incidence of this disease this year may be as great or greater than the average, it will be surprising if the death rate is not by far the lowest on record. This will be due to two main factors: first, that positive curative methods of treatment [specific serum and sulfapyridine] are available and second, that the medical profession in general is alive to the situation and knows the efficacy of these measures when applied early. Serum treatment has now been developed to such a degree that not only are specific sera for all types of pneumococci available but adequate dosage and methods of administration are well understood. It has been announced that for indigent patients serum will be provided free of charge by the State Department of Health. Sulfapyridine, too, has now been sufficiently studied so that its value and limitations are well recognized. If pneumonia this year proves to be anything like the fatal disease that it has been in the past it will be directly due to the failure of the medical profession to act and act quickly whenever a case of this disease is diagnosed or even suspected."

Rhode Island Hospital announces the appointment of two new interns, Dr Charles F. Begg and Dr Edward M. Gunn.

Memorial Hospital's Intern Alumni Clinic Day includes numerous teaching clinics, a symposium on pyelonephritis, peptic ulcer, luetic, congenital and bacterial heart diseases, and a clinical pathological conference of a 45-year-old housewife with intestinal obstruction, and gangrenous bowel possibly due to a ruptured Meckel's diverticulum.

The final book review of the year describes a new printing of Krafft-Ebing's text, *Psychopathia*

Sexualis, A Medico-forensic Study. This 626 page text sells for three dollars.

Twenty Five Years Ago (December, 1964)

A summary report of medical activities in Washington, prepared by the American Medical Association, details President Johnson's legislative program for health care [to be called "medicare"]. A policy paper issued by the White House, states: "First, we must provide adequate hospital and nursing home care for our senior citizens by a sound program financed through contributory social insurance. I pledge that the legislation to accomplish this will head my program next year." The major article in this issue is written by Robert F. Corrente, MD, and is entitled, "Gastro-intestinal Bleeding: Less Common Causes of Bleeding Must Be Considered in Every Case." Five cases of enteric bleeding are analysed. The first case describes a six-year-old male with an adenomatous polyp of the colon. The second patient is a 29-year-old woman with chronic, intermittent diarrhea. Studies suggested that the accompanying rectal bleeding was due to Butazolidin therapy. The third patient is a 62-year-old diabetic male who died as the result of a rare lesion: an arteriocholecholepseudoaneurysm [hemobilia]. The fourth patient is a 72-year-old women with cerebrovascular disease and rectal bleeding, possibly the result of an underlying colonic diverticulosis. The fifth case is a 43-year-old male with demonstrated bleeding duodenal ulcer. The patient was submitted to surgery, "... and was found to have a small, active duodenal ulcer ... but his duodenal disease did not seem sufficient to cause the degree of bleeding that had been observed. ... Exploration of the remainder of the abdomen revealed ... a benign leiomyoma of the gastric wall with the overlying mucosa showing three ulcerations, one of which had a blood clot at its base."

An article by John E. Fogarty, Congressman from the Second Rhode Island District is entitled, "Education Puts Knowledge to Work." Fogarty states, "These are exciting and dramatic years for anyone associated with bringing better health care to the American people. Never before have health professionals had so much to offer to so many. And never before have your services been so widely and urgently demanded."

The article continues: "But the health professions can render the full service of which they are capable only when the people they serve are taking active part in their own health protection. For every man or woman is, to a great extent, his own "health officer." The mother's decision determines whether or not her child is protected against polio or diphtheria. The father's decision to have a check-up makes possible the early diagnosis and cure of a hidden disease.

Fogarty concludes: "The health professions have no substitute for these individuals decisions. They can provide needed services. They can make these services conveniently available and economically accessible. But health is a very democratic commodity. It depends on the free actions of all of the people."

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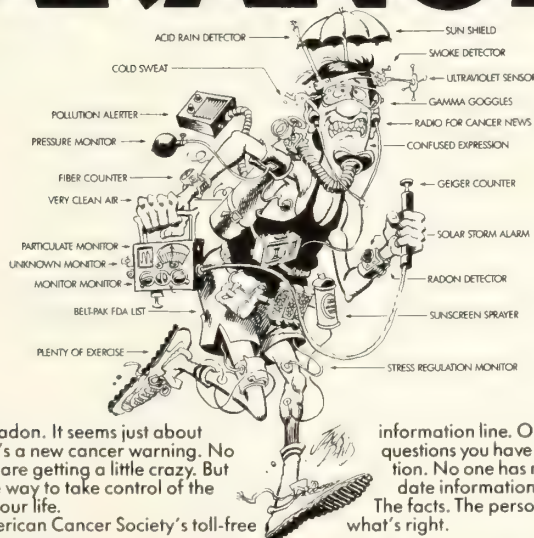
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Hypotension: Excessive hypotension is rare in uncomplicated hypertensive patients treated with VASOTEC alone. Heart failure patients given VASOTEC commonly have some reduction in blood pressure, especially with the first dose, but discontinuation of therapy for continuing symptomatic hypotension usually is not necessary when dosing instructions are followed; caution should be observed when initiating therapy. (See DOSAGE AND ADMINISTRATION.) Patients at risk for excessive hypotension, sometimes associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death, include those with the following conditions or characteristics: heart failure, hyponatremia, high-dose diuretic therapy, recent intensive diuresis or increase in diuretic dose, renal dialysis, or severe volume and/or salt depletion of any etiology. It may be advisable to eliminate the diuretic (except in heart failure patients), reduce the diuretic dose, or increase salt intake cautiously before initiating therapy with VASOTEC in patients at risk for excessive hypotension who are able to tolerate such adjustments. (See PRECAUTIONS, Drug Interactions and ADVERSE REACTIONS.) In patients at risk for excessive hypotension, therapy should be started under very close medical supervision and such patients should be followed closely for the first two weeks of treatment and whenever the dose of enalapril and/or diuretic is increased. Similar considerations may apply to patients with ischemic heart disease or cardiovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, receive an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further doses of VASOTEC, which usually can be given without difficulty once the blood pressure has stabilized. If symptomatic hypotension develops, a dose reduction or discontinuation of VASOTEC or concomitant diuretic may be necessary.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease. Available data from clinical trials of enalapril are insufficient to show that enalapril does not cause agranulocytosis at similar rates. Foreign marketing experience has revealed several cases of neutropenia or agranulocytosis in which a causal relationship to enalapril cannot be excluded. Periodic monitoring of white blood cell counts in patients with collagen vascular disease and renal disease should be considered.

Precautions: **General:** **Impaired Renal Function:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including VASOTEC, may be associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine were observed in 20% of patients. These increases were almost always reversible upon discontinuation of enalapril and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some patients with hypertension or heart failure with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when VASOTEC has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or VASOTEC may be required.

Evaluation of patients with hypertension or heart failure should always include assessment of renal function. (See DOSAGE AND ADMINISTRATION.)

Hyperkalemia: Elevated serum potassium (> 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was a cause of discontinuation of therapy in 0.28% of hypertensive patients. In clinical trials in heart failure, hyperkalemia was observed in 3.8% of patients, but was not a cause for discontinuation.

Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with VASOTEC. (See Drug Interactions.)

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, enalapril may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients:

Angioedema: Angioedema, including laryngeal edema, may occur especially following the first dose of enalapril. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to take no more drug until they have consulted with the prescribing physician.

Hypotension: Patients should be cautioned to report lightheadedness especially during the first few days of therapy. If actual syncope occurs, the patients should be told to discontinue the drug until they have consulted with the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) which may be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with enalapril is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions:

Hypotension: Patients on Diuretic Therapy: Patients on diuretics and especially those in whom diuretic therapy was recently instituted may occasionally experience an excessive reduction of blood pressure after initiation of therapy with enalapril. The possibility of hypotensive effects with enalapril can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with enalapril. If it is necessary to continue the diuretic, provide close medical supervision after the initial dose for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

Agents Causing Renin Release: The antihypertensive effect of VASOTEC is augmented by antihypertensive agents that cause renin release (e.g., diuretics).

Other Cardiovascular Agents: VASOTEC has been used concomitantly with beta-adrenergic-blocking agents, methyl-dopa, nitrates, calcium-blocking agents, hydralazine, prazosin, and digoxin without evidence of clinically significant adverse interactions.

Agents Increasing Serum Potassium: VASOTEC attenuates potassium loss caused by thiazide-type diuretics. Potassium-sparing diuretics (e.g., spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Therefore, if concomitant use of these agents is indicated because of demonstrated hypokalemia, they should be used with caution and with frequent monitoring of serum potassium. Potassium-sparing agents should generally not be used in patients with heart failure receiving VASOTEC.

Lithium: A few cases of lithium toxicity have been reported in patients receiving concomitant VASOTEC and lithium and were reversible upon discontinuation of both drugs. Although a causal relationship has not been established, it is recommended that caution be exercised when lithium is used concomitantly with VASOTEC and serum lithium levels should be monitored frequently.

Pregnancy—Category C: There was no fetotoxicity or teratogenicity in rats treated with up to 200 mg/kg/day of enalapril (333 times the maximum human dose). Fetotoxicity, expressed as a decrease in average fetal weight, occurred in rats given 1200 mg/kg/day of enalapril but did not occur when these animals were supplemented with saline. Enalapril was not teratogenic in rabbits. However, maternal and fetal toxicity occurred in some rabbits at doses of 1 mg/kg/day or more. Saline supplementation prevented the maternal and fetal toxicity seen at doses of 3 and 10 mg/kg/day, but not at 30 mg/kg/day (50 times the maximum human dose).

Radioactivity was found to cross the placenta following administration of labeled enalapril to pregnant hamsters.

There are no adequate and well-controlled studies of enalapril in pregnant women. However, data are available that show enalapril crosses the human placenta. Because the risk of fetal toxicity with the use of ACE inhibitors has not been clearly defined, VASOTEC® (Enalapril Maleate, MSD) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Postmarketing experience with all ACE inhibitors thus far suggests the following with regard to pregnancy outcome. Inadvertent exposure limited to the first trimester of pregnancy has not been reported to affect fetal outcome adversely. Fetal exposure during the second and third trimesters of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported, presumably representing decreased renal function in the fetus. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity such as patent ductus arteriosus have occurred in association with maternal use of ACE inhibitors, but it is not clear whether they are related to ACE inhibition, maternal hypotension, or the underlying prematurity.

Nursing Mothers: Milk in lactating rats contains radioactivity following administration of 14 C enalapril maleate. It is not known whether this drug is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when VASOTEC is given to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Adverse Reactions: VASOTEC has been evaluated for safety in more than 10,000 patients, including over 1000 patients treated for one year or more. VASOTEC has been found to be generally well tolerated in controlled clinical trials involving 2387 patients.

HYPERTENSION: The most frequent clinical adverse experiences in controlled trials were: headache (5.2%), dizziness (4.3%), and fatigue (3%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in controlled clinical trials were: diarrhea (1.4%), nausea (1.4%), rash (1.4%), cough (1.3%), orthostatic effects (1.2%), and asthenia (1.1%).

HEART FAILURE: The most frequent clinical adverse experiences in both controlled and uncontrolled trials were: dizziness (7.9%), hypotension (6.7%), orthostatic effects (2.2%), syncope (2.2%), cough (2.2%), chest pain (2.1%), and diarrhea (2.1%).

Other adverse experiences occurring in greater than 1% of patients treated with VASOTEC in both controlled and uncontrolled clinical trials were: fatigue (1.8%), headache (1.8%), abdominal pain (1.6%), asthenia (1.6%), orthostatic hypotension (1.6%), vertigo (1.6%), angina pectoris (1.5%), nausea (1.3%), vomiting (1.3%), bronchitis (1.3%), dyspnea (1.3%), urinary tract infection (1.3%), rash (1.3%), and myocardial infarction (1.2%).

Other serious clinical adverse experiences occurring since the drug was marketed or adverse experiences occurring in 0.5% to 1% of patients with hypertension or heart failure in clinical trials in order of decreasing severity within each category:

Cardiovascular: Cardiac arrest, myocardial infarction or cerebrovascular accident, possibly secondary to excessive hypotension in high-risk patients (see WARNINGS, Hypotension); cardiac arrest, pulmonary embolism and infarction, rhythm disturbances, atrial fibrillation, palpitation.

Digestive: Ileus, pancreatitis, hepatitis or cholestatic jaundice, melena, anorexia, dyspepsia, constipation, glossitis.

Neurological/Psychiatric: Depression, confusion, ataxia, somnolence, insomnia, nervousness, paresthesia.

Urogenital: Renal failure, oliguria, renal dysfunction (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Respiratory: Bronchospasm, rhinorrhea, asthma, upper respiratory infection.

Skin: Herpes zoster, pruritus, alopecia, flushing, photosensitivity.

Other: Vasculitis, muscle cramps, hyperhidrosis, impotence, blurred vision, taste alteration, tinnitus.

A symptom complex has been reported which may include fever, myalgia, and arthralgia; an elevated erythrocyte sedimentation rate may be present. Rash or other dermatologic manifestations may occur. These symptoms have disappeared after discontinuation of therapy.

Angioedema: Angioedema has been reported in patients receiving VASOTEC (0.2%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with VASOTEC should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Hypotension: In the hypertensive patients, hypotension occurred in 0.9% and syncope occurred in 0.5% of patients following the initial dose or during extended therapy. Hypotension or syncope was a cause for discontinuation of therapy in 0.1% of hypertensive patients. In heart failure patients, hypotension occurred in 6.7% and syncope occurred in 2.2% of patients. Hypotension or syncope was a cause for discontinuation of therapy in 1.9% of patients with heart failure. (See WARNINGS.)

Clinical Laboratory Test Findings:

Serum Electrolytes: Hyperkalemia (see PRECAUTIONS), hyponatremia.

Creatinine, Blood Urea Nitrogen: In controlled clinical trials, minor increases in blood urea nitrogen and serum creatinine, reversible upon discontinuation of therapy, were observed in about 0.2% of patients with essential hypertension treated with VASOTEC alone. Increases are more likely to occur in patients receiving concomitant diuretics or in patients with renal artery stenosis. (See PRECAUTIONS.) In patients with heart failure who were also receiving diuretics with or without digitalis, increases in blood urea nitrogen or serum creatinine, usually reversible upon discontinuation of VASOTEC and/or other concomitant diuretic therapy, were observed in about 11% of patients. Increases in blood urea nitrogen or creatinine were a cause for discontinuation in 1.2% of patients.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g and 1.0 vol %, respectively) occur frequently in either hypertension or heart failure patients treated with VASOTEC but are rarely of clinical importance unless another cause of anemia coexists. In clinical trials, less than 0.1% of patients discontinued therapy due to anemia.

Other (Causal Relationship Unknown): In marketing experience, rare cases of neutropenia, thrombocytopenia, and bone marrow depression have been reported.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin have occurred.

Dosage and Administration: **Hypertension:** In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally may occur following the initial dose of VASOTEC. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with VASOTEC to reduce the likelihood of hypotension. (See WARNINGS.) If the patient's blood pressure is not controlled with VASOTEC alone, diuretic therapy may be resumed.

If the diuretic cannot be discontinued, an initial dose of 2.5 mg should be used under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.)

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or in two divided doses. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. In such patients, an increase in dosage or twice-daily administration should be considered. If blood pressure is not controlled with VASOTEC alone, a diuretic may be added.

Concomitant administration of VASOTEC with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics may lead to increases of serum potassium (see PRECAUTIONS).

Dosage Adjustment in Hypertensive Patients with Renal Impairment: The usual dose of enalapril is recommended for patients with a creatinine clearance > 30 mL/min (serum creatinine of up to approximately 3 mg/dL). For patients with creatinine clearance ≤ 30 mL/min (serum creatinine ≥ 3 mg/dL), the first dose is 2.5 mg once daily. The dosage may be titrated upward until blood pressure is controlled or to a maximum of 40 mg daily.

Heart Failure: VASOTEC is indicated as adjunctive therapy with diuretics and digitalis. The recommended starting dose is 2.5 mg once daily. After the initial dose of VASOTEC, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. (See WARNINGS and PRECAUTIONS, Drug Interactions.) If possible, the dose of the diuretic should be reduced, which may diminish the likelihood of hypotension. The appearance of hypotension after the initial dose of VASOTEC does not preclude subsequent careful dose titration with the drug, following effective management of the hypotension. The usual therapeutic dosing range for the treatment of heart failure is 5 to 20 mg daily given in two divided doses. The maximum daily dose is 40 mg. Once-daily dosing has been effective in a controlled study, but nearly all patients in this study were given 40 mg, the maximum recommended daily dose, and there has been much more experience with twice-daily dosing. In addition, in a placebo-controlled study which demonstrated reduced mortality in patients with severe heart failure (NYHA Class IV), patients were treated with 2.5 to 40 mg per day of VASOTEC, almost always administered in two divided doses. (See CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects.) Dosage may be adjusted depending upon clinical or hemodynamic response. (See WARNINGS.)

Dosage Adjustment in Heart Failure Patients with Renal Impairment or Hyponatremia: In heart failure patients with hyponatremia (serum sodium < 130 mEq/L) or with serum creatinine > 1.6 mg/dL, therapy should be initiated at 2.5 mg daily under close medical supervision. (See DOSAGE AND ADMINISTRATION, Heart Failure, WARNINGS, and PRECAUTIONS, Drug Interactions.) The dose may be increased to 2.5 mg b.i.d., then 5 mg b.i.d. and higher as needed, usually at intervals of four days or more, if at the time of dosage adjustment there is not excessive hypotension or significant deterioration of renal function. The maximum daily dose is 40 mg.

For more detailed information, consult your MSD Representative or see Prescribing Information, Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19466. J6VS18R2(817)

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